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UGHJ

edited by Alessandro Boccanelli
and Laura Elena Pacifici Noja

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Grains of light

di Gian Stefano Spoto*

It is true, UGHJ is not a beautiful title for a journal. It doesn't sound well, no one will remember it, and, if it were to be published on Tv and on social media, no one would notice it. It is an awkward acronym for a publication that, moreover, defines itself as a grain of sand. A grain of sand is indeed minuscule, but it has a wonderful gift for refraction.

It is even more minuscule, and it is extremely hard to find the right angle. However, if we patiently look for it and discover it, the really subtle ray of light that UGHJ transmits will find receptors ready to share in paths, even the less beaten ones. These paths will serve to spread, among others, the idea of a right to health for everyone, a principle which we would like to draw away from the shade of demagogy, in a wish to dispel the taboos dear to the professional quitters.

Every publication has of course a director, and every director is a journalist. Especially when he/she is not also a scientist, he/she has to find encounter-clash meeting points with the scientific committee. While he/she would like to have scoops and paste-ups filled with the universe, they object that what is important is to find the latest topics for scientific, economic and political reflection in the pure (!) sense of the word. And maybe they are even right.

They are right because they firmly believe, together with the director, in a scientific journal whose words don't necessarily cover the globe but which fit in by capturing and conveying those impulse, original by virtue of their sensitivity and sense of commitment.

Most of all, we are never intent on leading battles alone. We would like to share and welcome suggestions from all parts of the world, hence establishing dialogues and collaborations.

As regards the grain of light, we would really like to replicate it and to distribute it to all those who have an eye for different angles.

* Editor-in-chief UGHJ.

Why this new journal?

by Alessandro Boccanelli, Laura Elena Pacifici Noja*

UGHJ comes into being during an extremely difficult time for humanity. However, as Bernard Henry Levy stated, it is in moments like these that "independence of spirit and intellectual salubrity are especially necessary". Covid-19, despite its gravity, has led us to face the urgency of personalized and participatory healthcare, a global domain unrestricted by national boundaries.

It is necessary to consider that, despite the existence of the Global Alliance for Vaccines and Immunization and of the Global Fund to Fight AIDS, TB and Malaria, pathologies other than Covid-19 have also recorded a significant increase on a global scale in the last two years. According to estimates by the World Health Organisation, an extra 2.9 million people compared to 2019 now suffer from TB, without the disease being diagnosed or recorded by the national health authorities.

The Global Health (GH) was led to broaden its gaze to a scope which goes beyond the traditional views on lifestyles and on the promotion of individuals' health. The prevalently descriptive nature of GH is transforming itself into a predictive one, hence oriented towards the prevention of multiple potential pathologies. The perspective of GH mandatorily includes the analysis of social, political, economic and environmental phenomena, placing them in the geographical context where they arise.

It is in this environment that the new UGHJ journal took place, with an inevitably interdisciplinary nature and covering themes which are complementary with one another. International health cooperation, social vulnerability, the great migratory flows and migrants' health, the vaccination issue, the use of new technologies in healthcare and their ethical impact – to cite only a few examples – are not independent variables. They are rather the building blocks of a single mosaic: that of global health. Every issue can be disassembled to conduct a more in-depth analysis of the single components, to then recompose it and obtain an overall view, in accordance with a recurring procedure in medical sciences.

One of the purposes of UGHJ is that of creating a tangible support system for those

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who will have to undertake changes and improvements in the healthcare sector. These include the decision makers, but also those in charge of giving advice and opinions, namely in the governance of priority-setting. Another objective, a more ambitious one if you will, is that of providing a "discussion room" to all those who consider global health to be one of the essential themes of our time.

The usefulness and vitality of the journal will depend on the imperative contribution not only of the world of academia and reseach, but also that of economics, business, healthcare and public administration, to the many sectors of which global health is comprised.

At the time we conceived the journal, the popular view was that the Coronavirus disease would be eradicated within a reasonable number of months and our intent, during the development phase, was that of dealing mainly with the Covid-19 aftermath. We now realise that the issues to be solved are still too many, and that it is impossible to do it within a short time frame. Our intention to deal with the post-Covid-19 phase ultimately remains, but we cannot exempt ourselves from publishing articles which narrate this battle in its development, a battle which we are all fighting.

Chronicles of a possible future

Reading into the pandemic and beyond

by Mario Braga, Flavia Riccardo*

Abstract
The emergence of a new virus (Sars-CoV-2) in 2019 and the consequent Covid-19 pandemic has had a devastating impact on societies and represents a moment of dramatic break and regression against the different issues posed by the SDG's. Dramatic consequences on a global level have been documented in terms of morbidity and mortality, both as direct and indirect effects of the Sars-CoV-2 infection, with profound consequences on economic progress, trust in governments, and social cohesion. This paper analyses the pandemic event from multiple angles specifically focussing on three mutually interconnected systems: healthcare, economies and society to try and identify elements that could shape possible post-pandemic evolution trends in policy and implementation models.

1. Introduction

The Sustainable Development Goals (UN-SDGs), are 17 goals with 169 targets that all UN Member States have agreed upon to work towards achieving by the year 2030[1]. These have represented and represent a consensus on how we would like to change the world in order to ensure human beings a better, more equitable, sustainable and environmentally friendly future. However, progress towards the achievement of most SDGs was already lagging behind in 2019 and the impact of the Covid-19 pandemic is expected to slow down and, in some cases, reverse difficultly achieved improvements[2,3]. Why it is so hard to progress towards something so widely accepted?

This has at least in part to do with the fact that these goals interconnect with numerous elements of the complex adaptive systems that we call "society". For example, local conflicts, international financial and economic flows, migrations, pollutions and the economic and social impact of trades have direct and indirect spill-over effects on each of the SDG's (Figure 1) and these, in turn, have a significant influence on each of these dimensions. This means, that achieving those goals inevitably impacts on lives and livelihoods, on conflicting priorities and interests consequently making their achievement less immediate. For this reason, documenting progress should not be taken for granted and recognised as a global achievement.

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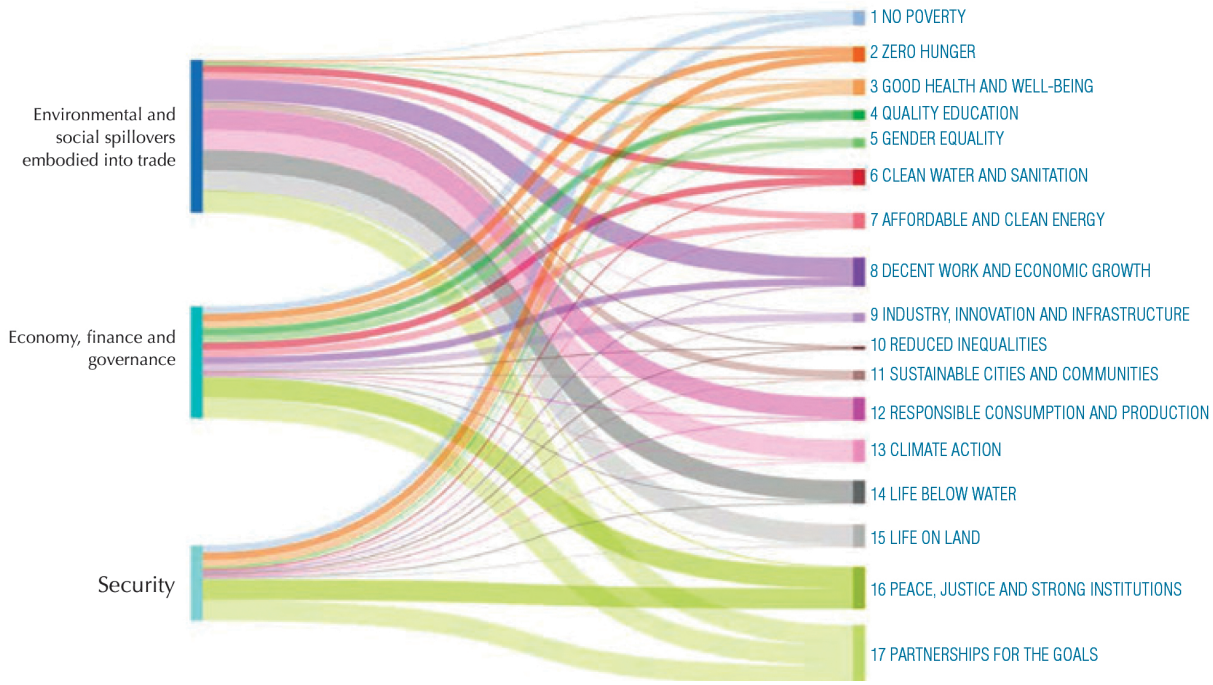

Fig. 1. Link between the three categories of spill-overs and the 17 SDGs. Source: Europe Sustainable Development Report 2020[4].

The emergence of a new virus (Sars-CoV-2) in 2019 and the consequent Covid-19 pandemic has had a devastating impact on those same societies and represents a moment of dramatic break and regression in the general statement represented by the different issues posed by the SDG's.

Firstly, the virus Sars-CoV-2 was hypothesised to be generated by a zoonotic jump (spill-over) from wildlife to humans, and the emergence of zoonotic disease is thought to be favoured by human activities such as encroachment into wildlife habitats as a consequence of expanding urbanization, cropland area and intensive animal farming[5].

Secondly, the pandemic emergency, which has almost reached two years of permanence, has highlighted the fragility of the health and social care systems of many countries, also the so called "economically developed" ones. It has also sadly documented how difficult it is to ensure, in these circumstances, the acquired levels of welfare and the respect for the fundamental rights of human beings, so well represented by the SDG's. Inequalities within and between countries have worsened and vulnerable and socially marginalized people have been able to access to a much lesser extent than the general population effective treatments or vaccination[6].

As has been pointed out by the "Sustainable Development Report 2021"[7]: "[...] The pandemic has impacted all three

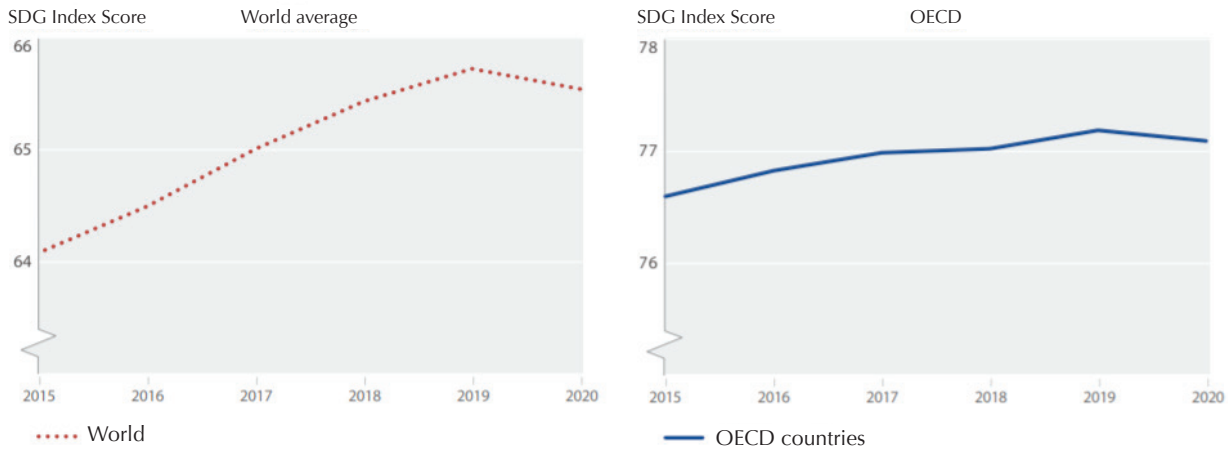

Fig. 2. Annual trend of the SDG index (World and OECD countries). Source: 2021 Sustainable Development Report[7]

dimensions of sustainable development: economic, social, and environmental. [...] There can be no sustainable development and economic recovery while the pandemic is raging".

This paper analyses the pandemic event from multiple angles specifically focussing on three mutually interconnected systems: healthcare, economies and society to try and identify elements that could shape possible post-pandemic evolution trends in policy and implementation models.

2. Pandemic complexity

As stated by Strumberg *at al.*, the Covid-19 pandemic has the characteristics of "a 'wicked problem': we have not seen it arrive, we suffer its effects, and it challenges our main stream of reasoning"[8]. The uncertainties that have characterized this crisis and the global spread of this new pathogen have not only highlighted the underlying fragility of our health systems, but also the intrinsic and often underlying dynamics that characterize the pillars upon which these systems are based. In addition, it highlighted how changes in part of the system, for example in health systems, affect the entire society through interconnections that are not always evident.

During this pandemic, for the first time since the adoption of the Sustainable Development Goals, the average global index of scores for the SDG's has declined[7]. Dramatic consequences on a global level have been documented in terms of morbidity and mortality[9], both as direct and indirect effects of the Sars-CoV-2 infection with profound consequences on economic progress, trust in governments, and social cohesion[10]. The degree of poverty of large sectors of the population has increased as a result[11], deepening the gap between the richest and the poorest both within individual countries and between countries[12]. A direct impact of the Covid-19 pandemic has also been recognized in the growth of global unemployment[13], of violence against vulnerable groups[14] and in the exposure

and exacerbation of existing human and civil rights violations[15,16]. All these impacts have been disproportionally higher in more fragile contexts and population groups as is immediately visible if the worsening trend of the SDG index is calculated globally and only among OECD countries, where it is still present but less evident (Figure 2).

3. Healthcare Systems

Healthcare systems were severely affected by the pandemic with the surfacing of weakness in the management of this emergency, especially regarding the primary and community care sector. However, more resilient healthcare systems were quickly able to adapt to the new situation with a strong acceleration in the introduction of new organizational models and an extensive use of digital technologies. The interaction between patients and healthcare professionals and between professionals have moved, when possible, online, bringing the healthcare sector closer to other sectors more mature in the use of digital resources (e.g. banking transactions, travel and hotel reservations, purchases).

This has also opened up the possibility of task shifting and changes in existing organizational models that led for example to the enrolment of pharmacies in vaccination campaigns[17], the transfer of cancer therapies from hospitals to home care[18], the strengthening of telemedicine and remote monitoring[19,20], the consolidation of community nurses[21], the spread of intermediate care[22], and to growing investments in community homes and community hospitals, which in turn could initiate profound changes in our health systems and, consequently, in our society.

Under this dramatic pressure, these changes and innovations have allowed our healthcare systems to react to the various pandemic waves. While the next challenge will be to accurately assess their positive and negative effects in ordinary conditions, it should be recognized that the ability to access timely an adequate volume of vaccines, i.e. to access the main public health response to the pandemic[23], has been inequitable across countries. Despite the COVAX initiative, promoted by numerous international public and private partners including the World Health Organization[24], to date only 5.7% of populations in low-income countries have received at least one dose of the Sars-CoV-2 virus vaccine[25].

4. Economies

The pandemic has led to a dramatic fall in global Gross Domestic Product (GDP) and the International Monetary Fund estimates that if Covid-19 were to have a prolonged impact into the medium term, it could reduce global GDP by a cumulative $5.3 trillion over the next five years[26]. However, the pandemic impacted differently across industrial sectors with IT companies, online commerce and logistics generally benefiting as opposed to other sectors (e.g. tourism, recreation, accommodation, food services) that were hit hard and will require longer time to recover[27]. Economic impact has also differed among people, with young people, women, unskilled workers and undeclared workers among mostly penalized categories, and between countries with an earlier recovery in China, for example, compared with Europe[28,29].

Different strategies in the application and enforcement

of public health measures impacted the economy, social life and wellbeing of people differently. Therefore, a second noteworthy element of analysis rotates around the differences in the non-pharmacological interventions put in place by countries to contrast the spread of infections and their level of implementation. This includes the timing, type, duration, and intensity of restrictions imposed on populations within countries and the dynamics of restrictions and controls regulating mobility between countries. A clear example is represented by Italy that transitioned from a national lock-down in the first acute epidemic phase to a tired sub-national closure approach. Although both approaches have been shown to be highly effective in reducing viral transmission and, consequently, the impact of Covid-19 on health services[30,31] the second approach was clearly associated with a smaller negative impact on the GDP[32].

Additional negative economic consequences at a global level were caused by the more or less drastic closure of borders that has continued throughout the extended duration of this emergency and are being enacted again at the time of writing with the emergence of the omicron virus variant[33]. Among the hardest hit sectors in this case were those with a strong segmentation of production in different countries (Global Value Chain). Additionally, particularly during the first epidemic wave, these restrictions strongly impacted on the mobility of researchers with a reduction in the capital of ideas generated. This was subsequently compensated by alternative methods of virtual interaction[34].

A recurring question that is being posed is what consequences this pandemic will have in the long term and how the supply and demand will change in different countries and among different population groups. Economic recovery, which began in the second half of 2021, appeared surprising in its speed and more sustained than expected, particularly if compared with the 2008 economic crash[29].

This momentum, if not broken by pandemic resurgences, particularly if associated with radical changes in the model of development and coupled with policies aimed at the future generations (such as the Next Generation EU plan[35]) could have very positive repercussions on collective well-being and on the creation of a more just and equitable post-pandemic society.

5. Societal inequities

As of 31 October 2021, UNESCO data from 210 countries showed that the median cumulative duration of partial or total school closures during the pandemic has been of 33 weeks (range 0-77 weeks)[36]. Even when alternative distance learning solutions were provided, it is still difficult to quantify the negative consequences of school closures. Considering existing global inequities in access to education, internet and digital literacy, the immediate impact on learning achievements as well as the longer term risk of exacerbating discrimination and inequality on a socio-economic and geographical basis should be considered. Further, school closures have been an obstacle for the development and the well-being of children and adolescents and have been associated with negative health impacts, including, but not limited to, mental health[37].

Gender inequities were also particularly evident during the Covid-19 pandemic. The female workforce was the most ex-

posed to negative consequences for several reasons. Firstly, because women are prevalent in work sectors at higher risk of exposure and burn-out including health care professions and professions caring for elderly and disabled people. Specifically, among healthcare workers, women were found to experience more frequent and intense symptoms of stress, anxiety, depression, sleep disturbance and burnout[38]. Secondly, because women were increasingly victims of violence and aggression in general and within homes[14] as economic and social stress coupled with restricted movement. Thirdly, because women's employment loss increased almost immediately during the pandemic. This was in part due to their relevant presence in occupational sectors that were more exposed to the crisis such as tourism, hospitality, education and childcare. However, it was also linked with an increased voluntarily drop out from employment[39] in a context in which women had to absorb an increased workload of unpaid activities such as childcare during school closures, family management, housework and home caring for elderly and/or disabled family members losing access to health and social services[40]. This has led to a 5% employment fall in 2020 among women, compared with 3.9% among men[13]. The loss of work among the female population has significant consequences for the well-being of the family that are likely to be on a long-term basis, given the greater difficulties women face in re-entering the work environment[40]. The disproportion of women in single parent families has further aggravated many of the aspects described above. Lastly, under those circumstances, the reduced or lack of access to health care services, the disruption of maternal health and family planning services and in the supply of modern contraceptives has particularly affected women, with a consequent increase in unwanted pregnancies, abortions, and maternal mortality[41,42].

A third element of social disparity[43] during the pandemic was triggered by the change in the employment sector with a widespread use of remote work, facilitated by the extensive use of IT technologies. This has exacerbated the gap between work from home jobs (often more highly skilled work categories) and those that require physical presence (often low-skilled jobs or jobs that require direct contact with clients) that were more difficult to maintain. Within this dynamic context, an increase in atypical jobs was observed which generated a reduction in revenues for Health Services in countries with financing systems based on social insurance and formal work contribution. Workers depending on whether they could work from home or not, lost income during lock-downs and changed their mobility patterns during more permissive epidemic phases. This means that the use of public and private transports and of urban and public spaces also changed leading to disparities also in the risk of exposure to Sars-CoV-2.

6. Fragments of Hope

Although not compensating the negative effects of the pandemic, in these complex and worrying circumstances, some signals can be interpreted positively.

Unlike what happened during the 2008 economic crisis, the Covid-19 pandemic has activated more sustained solidarity and participatory mechanisms. National governments have played an important role in many countries in protecting the social safety of those less equipped to bear the brunt of

the crisis. They did so by adopting financial and social protective mechanisms. Furthermore, governments of many high-income countries have directly intervened to protect national financial markets and national strategic companies against speculative and aggressive interventions and have directly and massively sponsored pharmaceutical research on innovation development. The latter was particularly evident for the development of vaccines against Sars-CoV-2 and has led to true technological innovations[44].

At the international level it is noteworthy to mention the work of the European Union which, overcoming deep divergences between Member States, decided to remove the budgetary constraints that severely limited individual country actions and policies, and adopted the following initiatives:

- Changed to the EU budget to address urgently the health and economic crisis.
- Redirected EU funds to help Member States with the greatest needs.
- Supported the most affected economic sectors.
- Negotiated and purchased vaccines for all Member States.
- Established the European instrument for temporary Support to mitigate Unemployment Risks in an Emergency (SURE)[45].
- Established the EU recovery plan, Next Generation EU[35].

These interventions, which mark a pro-social and solidarity "u-turn" of Member States compared with pre-pandemic prevailing narratives, strengthen the European Union and could pave the way for greater cohesion and important political changes at international as well as internal level.

Other positive elements can be traced in the accelerating momentum for life changing innovative processes with a strong presence of information technology spanning from health monitoring wearable devices to tools for molecular drug design[44]. The attitude towards public health systems has also changed. New value is being given once again to community and primary care, to the consolidation of public health and prevention as cornerstones to contrast the pandemic and in general the deterioration of global health, and to the strengthening of the concept of proximity in the provision of community health and social care.

During this emergency, healthcare systems have experienced new ways of working and implemented solutions that may well last beyond the pandemic itself. Even considering the evident and overwhelming negative impacts of the pandemic on the volumes and composition of healthcare services, which in some cases led to a reduction of up to 80% in elective surgeries, this crisis also forced health managers to consider whether all the things that were done in the past were necessary, appropriate, and just. Due to the increase in resource constrains, it was paramount to use available resources to support those services and procedures that would generate the greatest net benefit for patients prioritizing those in greatest need[46,47].

Some aspects, such as the environmental crisis, global warming, the depletion of natural resources and the loss of biodiversity will have to find an adequate and consistent response with a new development perspective that will also bring undoubted benefits to the health of future generations. Likewise, prevention and preparedness against global health threats that are expected to arise more frequently

because of these determinants will need policies framed around the need to address complexity and interconnectedness as is the case of the suggested One Health framework by the Global Health and Covid-19 Task Force of the 2021 G20 Presidency[48].

7. Concluding Remarks

An aphorism by W. Churchill states: "To improve means to change, to be perfect means to change often". We believe that it is of fundamental importance to exploit the learning opportunities that the dramatic crisis caused by the Covid-19 pandemic has offered.

Innovations that were projected to take place many years from now, faced an extraordinary acceleration. The spread in current practice of digital tools for remote monitoring and management of patients, the ability to organize effectively massive vaccination campaigns, the large public investment in medical research and innovation, which led to the development and approval of innovative vaccines and rapid diagnostic systems at an incredible speed, the immense production of knowledge and its open sharing, the growing importance of behavioural and public health interventions are just some examples of successes that can generate permanent changes in healthcare systems and in health care service delivery.

The need to define the global strategies for health and sustainable development was well understood by the WHO with the "Pan-European Commission on Health and Sustainable Development"[49], which produced a report were seven recommendations are identified, namely:

- Make the One Health concept operational at all levels.
- Take action at all levels of society to heal the divisions exacerbated by the pandemic.
- Support innovation to achieve better One Health.
- Invest in strong, resilient and inclusive national health systems.
- Create an enabling environment to promote investment in health.
- Improve health governance globally.
- Improve health governance in the pan-European region.

If these seven recommendations will be implemented, we will have capitalized on this crisis and will be able to look to the future with greater optimism. The WHO, the European Union and the Italian Ministry of Health have all recognized the conceptual framework of reference in the "One Health" approach, that is clearly consistent with the SDG targets and also declinable in other frameworks such as those specific for Urban Health[50].

We will need to restart after the pandemic and increase our efforts to achieve the SDG's, but it will necessary to do so also changing the way we live and produce, taking advantage of the innovations that have been made available at an increasing pace. When, at last, the post-pandemic phase will arrive, however, we will not be starting from scratch.

This said, it is undoubtable that some well-known challenges and old foes still lie ahead. One Health needs to be understood, integrated and, most of all, operationalized in practice to deliver its full potential, SDG's need to be re-prioritized in a new dimension of commitment and the positive changes that were introduced and implemented during the emergency capitalized upon to foster progress towards an equitably healthier world.

Notes

1. World Health Organization [website], *Sustainable Development Goals (SDGs)* [available at https://www.who.int/health-topics/sustainable-development-goals#tab=tab_1; latest access 17/11/2021].

2. Stronger collaboration for an equitable and resilient recovery towards the health-related Sustainable Development Goals: 2021 progress report on the Global Action Plan for Healthy Lives and Well-being for All. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO [available at https://apps.who.int/iris/handle/10665/341411; latest access 17/11/2021].

3. United Nations, *The Sustainable Development Goals Report*, 2020 [available at https://unstats.un.org/sdgs/report/2020/overview/; latest access 17/11/2021].

4. Europe Sustainable Development Report 2020 [available at https://eu-dashboards.sdgindex.org/chapters/part-1-performance-of-european-countries-against-the-sdgs; latest access 27/11/2021].

5. Rulli M.C., D'Odorico P., Galli N. (*et al.*), *Land-use change and the livestock revolution increase the risk of zoonotic coronavirus transmission from rhinolophid bats*, Nat Food 2, 2021, 409-416 [available at https://doi.org/10.1038/s43016-021-00285-x; latest access 27/11/2021].

6. Independent Panel for Pandemic Preparedness and Response (IPPPR), *Covid-19: Make it the Last Pandemic* [available at https://theindependentpanel.org/wp-content/uploads/2021/05/Covid-19-Make-it-the-Last-Pandemic_final.pdf; latest access 27/11/2021].

7. United Nations, *The Sustainable Development Goals Report*, 2021 [available at https://dashboards.sdgindex.org/chapters/executive-summary; latest access 27/11/2021].

8. Sturmberg J.P., Martin C.M., *Covid-19 – how a pandemic reveals that everything is connected to everything else*. J Eval Clin Pract, 2020;26(5):1361-1367, DOI:10.1111/jep.13419.

9. World Health Organization, *WHO Coronavirus (Covid-19) Dashboard* [available at https://covid19.who.int/; latest access 27/11/2021].

10. OECD [Website], *The impact of Covid-19 on health and health systems* [available at https://www.oecd.org/health/covid-19.htm; latest access 27/11/2021].

11. World Bank, Press Release, *Covid-19 to Add as Many as 150 Million Extreme Poor by 2021* [available at https://www.worldbank.org/en/news/press-release/2020/10/07/covid-19-to-add-as-many-as-150-million-extreme-poor-by-2021; latest access 27/11/2021].

12. Sánchez-Páramoruth C., Hill R., Gerszon Mahler D., Narayan A., Yonzan N., *Covid-19 leaves a legacy of rising poverty and widening inequality*, World Bank Blogs, 2021 [available at https://blogs.worldbank.org/development-talk/covid-19-leaves-legacy-rising-poverty-and-widening-inequality; latest access 27/11/2021].

13. United Nations, Press Release, *Covid crisis to push global unemployment over 200 million mark in 2022* [available at https://news.un.org/en/story/2021/06/1093182; latest access 27/11/2021].

14. UN Women, *Measuring the shadow pandemic: violence against women during Covid-19*, 2021 [available at https://reliefweb.int/sites/reliefweb.int/files/resources/Measuring-shadow-pandemic.pdf; latest access 27/11/2021].

15. The Danish Institute for Human Rights, *Covid-19 and human rights* [available at https://www.humanrights.dk/covid-19-human-rights; latest access 27/11/2021].

16. Civicus Monitor, *Country rating changes* [available at https://findings2020.monitor.civicus.org/rating-changes.html; latest access 27/11/2021].

17. Paudyal V., Fialová D., Henman M.C. (*et al.*), *Pharmacists' involvement in Covid-19 vaccination across Europe: a situational analysis of current practice and policy*, Int J Clin Pharm 43, 1139-1148, 2021 [available at https://doi.org/10.1007/s11096-021-01301-7].

18. Mittaine-Marzac B., Zogo A., Crusson J.C., Cheneau V., Pinel M.C., Brandely-Piat M.L., Amrani F., Havard L., Balladur E., Louissaint T., Nivet L., Ankri J., Aegerter P., De Stampa M., *Covid-19 outbreak: An experience to reappraise the role of hospital at home in the anti-cancer drug injection*, Cancer Med., 2021 Apr;10(7):2242-2249, DOI: 10.1002/cam4.3682. Epub 2021 Mar 5. PMID: 33665971; PMCID: PMC7982610.

19. Watson A.R., Wah R., Thamman R., *The Value of Remote Monitoring for the Covid-19 Pandemic*, Telemed J E Health, 2020 Sep; 26(9):1110-1112. DOI: 10.1089/tmj.2020.0134. Epub 2020 May 7. PMID: 32384251.

20. Smith A.C., Thomas E., Snoswell C.L. (*et al.*), *Telehealth for global emergencies: Implications for coronavirus disease 2019 (Covid-19)*, J Telemed Telecare. 2020;26(5):309-313. DOI:10.1177/1357633X20916567.

21. Yi X., Jamil N.B., Gaik I.T.C., Fee L.S., *Community nursing services during the Covid-19 pandemic: the Singapore experience*, Br J Community Nurs, 2020 Aug 2;25(8):390-395. DOI: 10.12968/bjcn.2020.25.8.390. PMID: 32757894.

22. Grosgurin O., Leidi A., Farhoumand P.D. (*et al.*), *Role of Intermediate Care Unit Admission and Noninvasive Respiratory Support during the Covid-19 Pandemic: A Retrospective Cohort Study*, Respiration, 2021;100(8):786-793. DOI:10.1159/000516329.

23. Meslé M.M., Brown J., Mook P., Hagan J., Pastore R., Bundle N., Spiteri G., Ravasi G., Nicolay N., Andrews N., Dykhanovska T., Mossong J., Sadkowska-Todys M., Nikiforova R., Riccardo F., Meijerink H., Mazagatos C., Kyncl J., McMenamin J., Melillo T., Kaoustou S., Lévy-Bruhl D., Haarhuis F., Rich R., Kall M., Nitzan D., Smallwood C., Pebody R.G., *Estimated number of deaths directly averted in people 60 years and older as a result of Covid-19 vaccination in the WHO European Region, December 2020 to November 2021*, Euro Surveill, 2021, Nov;26(47). DOI: 10.2807/1560-7917.ES.2021.26.47.2101021. PMID: 34823641.

24. Organizzazione Mondiale della sanità [website], *COVAX* [available at https://www.who.int/initiatives/act-accelerator/covax].

25. Our Wold in Data [website], *Coronavirus (Covid-19) Vaccinations*, [available at https://ourworldindata.org/covid-vaccinations].

26. International Monetary Fund, *World economic outlook 2021* [available at https://www.imf.org/en/Publications/WEO/Issues/2021/10/12/world-economic-outlook-october-2021; latest access 27/11/2021].

27. McKinsey & Company [website], *Covid-19 recovery in hardest-hit sectors could take more than 5 years* [available at https://www.mckinsey.com/featured-insights/coronavirus-leading-through-the-crisis/charting-the-path-to-the-next-normal/covid-19-recovery-in-hardest-hit-sectors-could-take-more-than-5-years; latest access 27/11/2021].

28. OECD 2021, *Informality and Covid-19 in Eurasia: The Sudden Loss of a Social Buffer*, OECD Publishing, Paris [available at https://www.oecd.org/eurasia/Covid-19-informality-Eurasia.pdf; latest access 29/11/2021].

29. OECD 2021, *The Territorial Impact of Covid-19: Managing the Crisis and Recovery across Levels of Government*, OECD Policy Responses to Coronavirus, OECD Publishing, Paris [available at https://read.oecd-ilibrary.org/view/?ref=1095_1095253-immbko5x-b7&title=The-territorial-impact-of-Covid-19-Managing-the-crisis-and-recovery-across-levels-of-government&_ga=2.93550805.999755777.1638186323-2129290222.1638186323; latest access 29/11/2021].

30. Guzzetta G., Riccardo F., Marziano V., Poletti P., Trentini F., Bella A., Andrianou X., Del Manso M., Fabiani M., Bellino S., Boros S., Urdiales A.M., Vescio M.F., Piccioli A., Covid-19 Working Group 2, Brusaferro S., Rezza G., Pezzotti P., Ajelli M., Merler S., *Impact of a Nationwide Lockdown on Sars-CoV-2 Transmissibility*, Italy, Emerg Infect Dis., 2021, Jan;27(1):267–70. DOI: 10.3201/eid2701.202114. Epub 2020 Oct 20. PMID: 33080168; PMCID: PMC7774526.

31. Manica M., Guzzetta G., Riccardo F., Valenti A., Poletti P., Marziano V., Trentini F., Andrianou X., Mateo-Urdiales A., Del Manso M., Fabiani M., Vescio M.F., Spuri M., Petrone D., Bella A., Iavicoli S., Ajelli M., Brusaferro S., Pezzotti P., Merler S., *Impact of tiered restrictions on human activities and the epidemiology of the second wave of Covid-19 in Italy*, Nat Commun. 2021 Jul 27;12(1):4570. DOI: 10.1038/s41467-021-24832-z. PMID: 34315899; PMCID: PMC8316570.

32. OECD Economic Survey of Italy, September 2021 [available at https://www.oecd.org/economy/italy-economic-snapshot/].

33. The New York Times, *As Omicron Variant Circles the Globe, African Nations Face Blame and Bans* [available at https://www.nytimes.com/2021/11/27/world/africa/coronavirus-omicron-africa.html; latest access 27/11/2021].

34. Donthu N., Gustafsson A., *Effects of Covid-19 on business and research*, J Bus Res. 2020;117:284-289. DOI:10.1016/j.jbusres.2020.06.008.

35. European Commission [website], *Recovery Plan for Europe* [available at https://ec.europa.eu/info/strategy/recovery-plan-europe_en; latest access 27/11/2021].

36. UNESCO, *Education: From disruption to recovery* [available at https://en.unesco.org/covid19/educationresponse; latest access 27/11/2021].

37. Chaabane S., Doraiswamy S., Chaabna K., Mamtani R., Cheema S., *The Impact of Covid-19 School Closure on Child and Adolescent Health: A Rapid Systematic Review*. Children (Basel), 2021, May 19;8(5):415. DOI: 10.3390/children8050415. PMID: 34069468; PMCID: PMC8159143.

38. Danet A., *Psychological impact of Covid-19 pandemic in Western frontline healthcare professionals*, A systematic review, Med Clin (Engl Ed). 2021;156(9):449-458. DOI:10.1016/j.medcle.2020.11.003.

39. McKinsey & Company [website], *Seven charts that show Covid-19's impact on women's employment* [available at https://www.mckinsey.com/featured-insights/diversity-and-inclusion/seven-charts-that-show-covid-19s-impact-on-womens-employment; latest access 27/11/2021].

40. UN Policy Brief, *The Impact of Covid-19 on Women* [available at https://www.unwomen.org/-/media/headquarters/attachments/sections/library/publications/2020/policy-brief-the-impact-of-covid-19-on-women-en.pdf?la=en&vs=1406].

41. Kumar N., *Covid 19 era: a beginning of upsurge in unwanted pregnancies, unmet need for contraception and other women related issues*, Eur J Contracept Reprod Health Care, 2020 Aug;25(4):323-325. DOI: 10.1080/13625187.2020.1777398. Epub 2020 Jun 22. PMID: 32567961.

42. UNFPA Maldives, *The impact of Covid-19 on maternal health and family planning in Maldives* [available at https://reliefweb.int/sites/reliefweb.int/files/resources/unfpa_covid19_impact_fina.pdf; latest access 28/11/2021).

43. United Nations, 2020, *The social challenge in times of Covid-19* [available at https://repositorio.cepal.org/bitstream/handle/11362/45544/1/S2000324_en.pdf).

44. The Conversation [Website], *Three medical innovations fueled by Covid-19 that will outlast the pandemic*, 2021 [available at https://theconversation.com/3-medical-innovations-fueled-by-covid-19-that-will-outlast-the-pandemic-156464; latest access 28/11/2021].

45. European Commission [Website], *The European instrument for temporary Support to mitigate Unemployment Risks in an Emergency (SURE)* [available at https://ec.europa.eu/info/business-economy-euro/economic-and-fiscal-policy-coordination/financial-assistance-eu/funding-mechanisms-and-facilities/sure_en; latest access 28/11/2021].

46. Clarke M., Born K., Johansson M., Jørgensen K.J., Levinson W., Madrid E., Muscat Meng D., Ariel Franco J.V., *Making wise choices about low-value health care in the Covid-19 pandemic*, Cochrane Database of Systematic Reviews 2021;(9):ED000153 https://doi.org/10.1002/14651858.ED000153.

47. Emanuel E.J., Govind Persad G., Upshur R., Thome B., Parker M. (*et al.*), *Fair allocation of scarce medical resources in the time of Covid-19*, New England Journal of Medicine 2020;382:2049–55. https://doi.org/10.1056/NEJMsb2005114.

48. G20, Task Force 1 Global Health and Covid-19, Policy Brief, *One health-based conceptual frameworks for comprehensive and coordinated prevention and preparedness plans addressing global health threats*, September 2021 [available at https://www.t20italy.org/wp-content/uploads/2021/09/TF1_PB05_LM02.pdf; latest access 28/11/2021].

49. Pan-European Commission on Health and Sustainable Development, Report, *Drawing light from the pandemic: a new strategy for health and sustainable development*, September 2021 [available at https://www.euro.who.int/__data/assets/pdf_file/0015/511701/Pan-European-Commission-health-sustainable-development-eng.pdf; latest access 28/11/2021].

50. Ramirez-Rubio O., Daher C., Fanjul G., Gascon M., Mueller N., Pajín L., Plasencia A., Rojas-Rueda D., Thondoo M., Nieuwenhuijsen M.J., *Urban health: an example of a "health in all policies" approach in the context of SDGs implementation*. Globalization and Health (2019) 15:87 https://doi.org/10.1186/s12992-019-0529-z.

Patents and the Covid-19 vaccines

by Vincenzo Denicolò*

Abstract
The Covid-19 pandemic has shown that our pharmaceutical innovation system is capable of delivering results, but it has also highlighted the possibility of a new model of innovation, in which the gap between basic and applied research is getting smaller and smaller. An analysis of the topic is provided to offer an overview and stimulate debate.

1. Introduction

The Covid-19 pandemic has posed a major challenge on the pharmaceutical innovation system.

In 2020, extensive lockdowns were the only effective tool to contain the spread of the virus. In that year, the pandemic claimed 2 million lives and caused a massive worldwide recession. Governments faced a tragic trade-off between public health and national income and were desperate for effective treatments. Any medical innovation that could help prevent or cure the disease was regarded as invaluable.

With so much at stake, the pharmaceutical innovation system undeniably delivered. The first Covid-19 vaccine was approved in December 2020, just 10 months after the breakout of the pandemic. (By way of comparison, the average time needed for the approval of new drugs exceeds 10 years). In the following months, several other vaccines have become available. More recently, antiviral drugs have been developed that seem effective against the Covid-19 disease, and they too are being approved at record speed.

Naturally, the production capacity for Covid-19 vaccines was small at first. In the first half of 2021, even rich countries struggled to procure the vaccines, and the poor ones were almost completely excluded. In a few months, however, things have changed. By the end of 2021, more than 10 billion doses will have been produced worldwide.

Today, rich countries have enough doses to vaccinate their entire population, and vaccines have started to be delivered to middle-income and poor countries.

As vaccination campaigns proceed, economies are recov-

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ering. In many regions, national income will have returned to the pre-pandemic levels by the end of 2021, or at most in the first semester of 2022.

This sounds like a success story. Yet, the Covid-19 pandemic has prompted a heated debate on pharmaceutical innovation and the way it is organized and promoted. At the center of this debate is the role of the intellectual property protection granted to vaccines and drugs. Commentators, scholars, and governments have proposed a waiver of intellectual property rights on Covid-19 vaccines and the new antiviral drugs that will be available soon. So far, however, no such waiver has been agreed on.

This article reviews the policy debate and discusses possible reforms of the current system of pharmaceutical innovation.

2. The social costs of patents

A patent gives an inventor the exclusive right to manufacture, use or sell the invention for a period of time, which is usually 20 years from the date of patent application. This exclusivity period often confers to the inventor some market power. When this market power is exercised with the goal of maximizing the inventor's profit, it generally results in a contraction of output and an increase in prices. The contraction of output means that consumers will consume less, and the increase in prices means that they will pay more for what they consume. These effects represent the main social costs of patents.

2.1. *Rich countries*

In rich countries, the social costs of patents on Covid-19 vaccines have been mild in comparison to other pharmaceutical patents and to the value of the vaccines. To substantiate this claim, I consider in turn the price and output effects of the patents on Covid-19 vaccines.

a. Price

Patents on new drugs sometimes result in exorbitant prices that may significantly limit access to the medicines. For example, when the hepatitis-C drug *sofosbuvir* was first launched in 2013, it was priced at more than $80,000 per treatment. With a production cost estimated at less than $150, this represented a price-cost margin of over 50,000%.

In the case of the Covid-19 vaccines, price-cost margins appear to be much lower. Although the exact costs of production per dose are unknown, a reasonable estimate puts them in the range of €1-3. As for prices, they vary from vaccine to vaccine. The Oxford/AstraZeneca vaccine is allegedly priced at cost as per contractual clauses imposed by the University of Oxford on AstraZeneca. The price is, indeed, around €3 per dose. The Janssen vaccine is priced at around €7 per dose, with a price-cost margin in the order of 100%. The main mRNA vaccines, Moderna and BioNTech/Pfizer, are more expensive. For example, the Moderna price is now reportedly close to €25 per dose, which would translate into a price-cost margin of about 1,000%. This is high, but it is 50 times lower than that of *sofosbuvir*.

In view of the huge social value of the vaccines, these prices are all but exploitative. For a country such as Italy, which by the end of 2021 will have purchased around 100 million doses, the total expenditure will be less than €2 billion. This is approximately the same economic cost as just *one week* of the relatively mild lockdown we experienced in the spring of 2021. It therefore

appears that the economic benefits of the vaccines are a large multiple of the costs, even without including into the calculation the value of saved human lives. No doubt, Italy would have been prepared to pay for the vaccines much more than it actually paid.

One wonders why then prices are not higher. There are several possible answers to this question. First, the Oxford/AstraZeneca vaccine is priced at cost at the request of the University of Oxford, which originally developed the vaccine. Likewise, other vaccines received substantial public funds on the explicit or implicit understanding that the price would have been kept at reasonable levels. Second, from the outset several vaccines have been competing with one another. This competition is possible because patents are relatively narrow and confer exclusive property rights over a specific vaccine, not on all Covid-19 vaccines. Third, pharmaceutical companies may voluntarily restrain their pricing for fear of regulatory intervention in the form, for instance, of compulsory licensing, or of a suspension of patent rights[9].

b. Output

In the spring of 2021, with several Covid-19 vaccines already approved, even rich countries still struggled to procure the vaccines. Some commentators blamed patents for the scarcity of vaccines, on the grounds that one of the effects of patents is precisely the contraction of output.

But in fact, high prices and low output are the flip sides of the same coin: the patent holder contracts output only to the extent that this is necessary to keep the price at the target level. In other words, once prices are set, pharmaceutical companies have no reason to ration demand. They would have no incentive to ration even under monopoly, but this is true *a fortiori* when there is some competition among the firms, as the demand that a firm does not meet will then be satisfied by its competitors.

The initial shortage of vaccines was not, therefore, a strategic choice of pharmaceutical companies. The simple truth is these companies needed time to scale up production. Even though the manufacturing process was initiated even before the vaccines were approved, expanding the output took time because the production of vaccines is a complex endeavor, especially for the mRNA vaccines that rely on a very innovative technology. In a few months, however, production capacity has been enlarged and now in rich countries there is no shortage of vaccines.

One may wonder whether the increase in production could have been faster in the absence of patent protection. The answer is probably no. In the very short run, patents are not a crucial factor: inventors are already protected by "lead time" advantages, i.e., the simple fact that imitation takes time. Even when there are no legal barriers to the exploitation of the innovative technological knowledge, that is to say, learning to practice an innovation may be no easy task because of the need to acquire so-called tacit knowledge. Think, for instance, of the difficulty of learning new surgery techniques even if they have been described in the medical literature. (Incidentally, this explains why no firm other than Moderna has yet tried to manufacture the Moderna vaccine even though Moderna stated that it would not enforce its patents for some time).

Therefore, it seems unlikely that suspending patent rights could have helped increase the production of Covid-19 vaccines in 2021. Any expansionary effect on output would have probably taken more time.

2.2. *Poor countries*

In the previous subsection, I have argued that the prices of Covid-19 vaccines have not effectively restricted access to the treatment in rich countries. Today, all Italians, Germans and British who want to be vaccinated can get their shots almost instantly. When it comes to poor countries, however, the situation is more complicated.

In Uganda, for instance, per-capita health expenditure is about $50 per year. Purchasing the mRNA vaccines (which are, arguably, the best performing ones) at the current prices would pose a significant burden on Uganda's national health system. In addition, vaccines must be delivered to the population, and this poses further challenges in countries where sanitary infrastructures are rudimentary. It therefore comes as no surprise that only 1% of Uganda's population has been vaccinated so far.

In fact, the rate of vaccination is below 10% in most African countries, and it is just 25% even in a middle-income country such as India. Even though other factors may also play a role, it seems that a reduction in the price of the vaccines may be an important element of a successful vaccination campaign in developing countries. To the extent that patents prevent such a reduction, they may impose social costs that are not as limited as those borne by rich countries.

3. Remedies

What can policy do to facilitate access to Covid-19 vaccines in poor countries? This section discusses three possible strategies, which are presented in increasing order of patent-rights weakening.

3.1. *Voluntary practices*

The first strategy relies on the goodwill of pharmaceutical companies and rich-country governments. It calls for these governments to donate millions of doses to poor countries, and for pharmaceutical companies to selectively reduce the price of the vaccines in poor or middle-income countries.

In fact, these actions could be carried out even by non-altruistic agents. Given the ease of transmission of the Covid-19 virus, and the fact that the protection afforded by the vaccines is limited, vaccinating as much as possible of the world population is also in the self-interest of the rich countries. The donations of vaccines may therefore be regarded as an investment in public health by donating countries.

As for the pharmaceutical companies, the profit foregone by selectively reducing the price in middle-income or poor countries is probably small, perhaps even non-existent. For one thing, in the case of the Covid-19 vaccines the risk of parallel trade is limited, as vaccines are purchased almost exclusively by governments and public institutions. For another thing, charging different prices in different countries is a common marketing strategy, called price discrimination, which may well be profitable for the seller. One could therefore say, paraphrasing Adam Smith, that "it is not from the benevolence of the pharmaceutical companies that the poor countries may expect their vaccines but from their regard to their own self-interest".

Nevertheless, some commentators doubt that these voluntary practices may suffice to provide enough vaccines for the entire world population. More interventionist strategies have therefore been proposed.

3.2. *Compulsory licensing*

Compulsory licensing is when a government authorizes the production of a patented product even without the consent of the patent holder. Under the TRIPS agreements of 1994, compulsory licensing is permitted under some conditions. The most frequently invoked reason for compulsory licensing is public health, and there is little doubt that the Covid-19 pandemic would be a valid justification.

Therefore, a country such as India, for instance, can invoke the TRIPS agreements and right now ask for a compulsory licensing of the patents that protect the Covid-19 vaccines. If the compulsory license is agreed upon by the World Trade Organization (WTO), Indian firms could then produce the vaccines upon payment of a "reasonable royalty" to the patent holders – a royalty that would likely be quite low. Under the Doha Declaration of 2001, Indian firms could even export the vaccines to other countries that lack the technological capabilities to manufacture the vaccines and have also requested a compulsory license. However, Indian firms could not export the vaccines to other countries.

There is much to say in favor of this solution. An extensive application of compulsory licensing would be an effective way of reducing the price of vaccines in poor countries, leaving a substantial profit margin in the rich ones. The profits reaped in rich countries could allow the pharmaceutical companies to recoup their R&D costs. This solution could therefore represent a reasonable compromise between the goal of guaranteeing access to the vaccines and that of incentivizing the research on innovative drugs.

3.3. *Waiving intellectual property rights*

In October 2020, India and South Africa proposed a waiver of intellectual property rights on Covid-19 vaccines and drugs for the duration of the epidemic. Various countries, including the US, have backed this proposal. Other countries, however, are against it. The proposal is unlikely to be approved as this requires a qualified majority of countries, but nevertheless it has been extensively debated.

There are two main differences between compulsory licensing and a waiver of intellectual property rights. The first one is relatively minor: with a waiver, producers of generics will not have to pay any royalty to patent holders. Since the reasonable royalties to be paid in case of compulsory licensing are small, however, this factor seems to be of secondary importance. A more relevant difference is that a waiver of Covid-19 related patents would allow the production or import of generics also in rich countries. As noted, this would probably have little impact in the very short run, but in the longer run it could erode the patent holders' profit margins.

The problem with a waiver of patent rights is that it will significantly impair the incentives to innovate. Inventing new vaccines or new drugs is a very risky and costly endeavor. In the market economies we live in, drug innovation is largely delegated to private companies that seek to maximize their profits rather than the common good. So, who

would invest in the search for new drugs without the prospect of recouping the R&D costs and making a profit?

The need of incentivizing the investments in R&D was indeed acutely felt before the vaccines were developed, to the point that various governments entered in "advance purchase agreements" with companies holding promising candidates and directly funded some of them. Now that several vaccines are available, it may seem natural to put more emphasis on the issue of the access to the treatment. However, this approach is short-sighted. The Covid-19 pandemic may not be the last one, and we must preserve the incentives to invest in the search for the next vaccines.

More generally, it is always efficient to waive patent rights *ex post*, after the innovation has been achieved. A forward-looking policy, however, must take an *ex-ante* perspective, as if the innovation were yet to come. To put it differently, society must strike a balance between the goals of encouraging innovation on the one hand, and the diffusion of the new products on the other hand. A waiver of intellectual property rights puts all the weight on the goal of diffusion. But if the incentives to innovate are destroyed, there will be no innovative technologies to be diffused.

4. Rethinking pharmaceutical innovation

So far, I have argued that our pharmaceutical innovation system has performed well in the Covid-19 pandemic. The social costs of patents have been relatively mild, and they can be further limited within the existing institutional framework by the adoption of sensible policies.

Still, one may wonder why such an important task as that of developing new drugs is being delegated to market forces. Is a different system feasible?

To answer that question, it may be useful to note a striking feature of the development of Covid-19 vaccines, i.e., the limited role played by the so-called "big pharma". The AstraZeneca vaccine was designed by a team of researchers at the University of Oxford, and the pharmaceutical company entered into play only at the stage of clinical tests. The same is true of Pfizer with the BioNTech vaccine. Moderna and BioNTech are both, effectively, university spin-offs. Of the four major vaccines used in western countries, only the Janssen vaccine has been developed entirely by a big pharmaceutical company.

Leaving the clinical testing aside, it seems that universities and public research centers possessed all the technological capabilities required to develop the vaccines on their own. This is probably true, to some extent, of many other drugs. For example, *sofosbuvir* was invented at Pharmasset, a small pharmaceutical company founded by scientists from Emory University. Only later was Pharmasset bought by Gilead, which completed the clinical tests and commercialized the drug.

Compared to the traditional picture where pharmaceutical companies do all the R&D, a new pattern seems to emerge here. When basic scientific research shows some promise of pharmacological applications, scientists tend to leave the academy, patent the results of their scientific research, and create their own spin-offs to conduct more applied research. And when this more applied research succeeds, resulting in candidate drugs that are ready for the clinical tests, the spin-

offs enter in joint ventures with bigger pharmaceutical companies, or are acquired by them. The big companies conduct the tests and commercialize the product.

In other words, there seems to be a closer and closer relationship between basic scientific research and the design of new drugs, and the comparative advantage of big pharmaceutical companies seems to be more and more limited to the stage of clinical testing.

If this is so, then a new model of pharmaceutical innovation seems possible. In this new model, private companies would play a much more limited role than they do today. This would reduce or eliminate the many distortions that market forces may create in a sector such as the pharmaceutical one.

The first step towards the implementation of the new model is the abolition of patents on drugs. This would stop the hemorrhage of scientists from universities and public research centers to for-profit spin-offs created *ad hoc*. Without the protection of patents, scientists would have much less incentives to leave the academy; they would continue their research there.

The second step is the creation of incentives for universities and public research centers to engage into more applied research, bridging the remaining gap between purely academic research and the design of new drugs. This is probably the most critical part of the suggested reform. It raises several specific issues, which will not be analyzed here.

The third step is the nationalization of the clinical testing. Clinical tests are already heavily regulated and are often hosted in public hospitals or public health institutions. Nationalizing the entire process seems therefore relatively simple. It could create big efficiencies, eliminating the conflicts of interests between the owners of drug candidates, the doctors who are engaged in the testing, and the regulatory agencies.

Pharmaceutical companies would be responsible only for the manufacturing of the drugs. With no patent protection, all drugs would be generics. The pharmaceutical sector would be highly competitive, and the prices of new drugs would be close to production costs.

5. Conclusion

The Covid-19 pandemic has shown that our pharmaceutical innovation system can deliver, but it has also exposed a new pattern of innovation, where the gap between basic and applied research is getting smaller and smaller. This suggests that we could adopt a different system, which is not based on market forces and intellectual property rights. Perhaps the suggested reform is utopian, but it has the potential to reduce the many inefficiencies created by our current system of pharmaceutical innovation.

Notes

1. DiMasi J.A., Grabowski H.G., Hansen R.W., *Innovation in the pharmaceutical industry: New estimates of R&D costs*, J Health Econ, 2016, May; 47:20-33. DOI: 10.1016/j.jhealeco.2016.01.012.

2. See Vaccine Manufacturing, *Launch and Scale Speedometer* [available at https://launchandscalefaster.org/covid-19/vaccinemanufacturing; latest access 14/11/2121].

3. In return, the inventor must disclose the innovation fully. In pharmaceuticals, the effective life of patents is typically shorter than the statutory term of 20 years because of the time needed to pass the pre-clinical and clinical tests that are necessary to get regulatory approval. As noted, the development of a new drug takes on average more than 10 years. For this reason, in most countries there exist special provisions that extend the duration of pharmaceutical patents for some time. Even accounting for these extensions, however, the average effective patent life in pharmaceuticals is around 12 years: see, e.g., Grabowski H., Long G., Mortimer R. (2014), *Recent trends in brand-name and generic drug competition*, Journal of medical economics, 17(3), 207-214. This issue however is largely irrelevant for the Covid-19 vaccines. Given their extraordinarily fast approval, their effective patent life will be close to 20 years.

4. See the 2015 *Report of the Committee on Finance of the US Senate, The Price of Sovaldi and Its Impact on the U.S. Health Care System* [available at https://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf; latest access 30/11/2021].

5. See Hill A., Khoo S., Fortunak J., Simmons B., Ford N. (2014), *Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clinical Infectious Diseases*, 58(7), 928-936. Their estimate of the unit production cost of *sofosbuvir* is in the range of $68-136.

6. See Light D.W., Lexchin J., *The costs of coronavirus vaccines and their pricing*, J R Soc Med., 2021, November; 114(11):502-504; DOI: 10.1177/01410768211053006, which actually places the cost at less than $1 but probably underestimates the true cost. Note that this is the unit production cost, which does not include the costs of developing the vaccine.

7. For a more systematic attempt at quantifying the economic value of the vaccines for the US, see Padula W.V., Malaviya S., Reid N.M., Cohen B.G., Chingcuanco F., Ballreich J., Alexander G.C. (2021), *Economic value of vaccines to address the Covid-19 pandemic: a US cost-effectiveness and budget impact analysis*. Journal of Medical Economics, 24(1), 1060-1069.

8. For example, the price of the hepatitis-C drugs fell substantially as new competing drugs were brought to the market: see, for instance, Barber M.J., Gotham D., Khwairakpam G., Hill A. (2020), *Price of a hepatitis C cure: Cost of production and current prices for direct-acting antivirals in 50 countries*, Journal of Virus Eradication, 6(3), 100001.

9. In fact, a single vaccine may be protected by a number of different patents, each of which covers a specific innovative component of the vaccine. For example, Moderna claims that it holds at least seven patents that protect its vaccine. On the other hand, other patents may read on more than one vaccine. For example, all mRNA vaccines exploit a technology patented by the University of Pennsylvania, which modifies the mRNA so that it does not trigger a response by the immune system. Both Moderna and BioNTech have sub-licensed the patents that protect this technology from a licensee of the University of Pennsylvania. See Gaviria M., Kilic B. (2021), *A network analysis of Covid-19 mRNA vaccine patents*, Nature Biotechnology, 39, 546-548.

10. This explanation is sometimes referred to as the "regulatory pre-emption theory".

11. In principle, there could be another, subtler reason for the relatively low prices, which has to do with the so-called "Coase conjecture". Since vaccines are, at least partially, a durable good, even a monopolist faces the competition of its own future supply: see Coase R.H. (1972), *Durability and monopoly*, The Journal of Law and Economics, 15(1), 143-149. Under some conditions, this implies that prices should immediately fall at the competitive level. In practice, however, given buyers' impatience and firms' capacity constraints, it seems unlikely that this effect may have played a significant role.

12. See, for instance, Kisby T., Yilmazer A., Kostarelos K. (2021), *Reasons for success and lessons learnt from nanoscale vaccines against Covid-19*, Nature Nanotechnology, 16(8), 843-850.

13. On the importance of lead time, see Cohen W.M., Nelson R., Walsh J.P. (2000), *Protecting their intellectual assets: Appropriability conditions and why US manufacturing firms patent (or not)*, NBER WP 7552.

14. See Coronavirus (Covid-19) Vaccinations, Statistics and Research, Our World in Data [available at https://ourworldindata.org/covid-vaccinations; latest access 14/11/2121].

15. The risk of parallel trade is often regarded as the main reason why pharmaceutical companies refrain from

reducing prices in poor countries. Parallel trade is the practice of buying products in countries where they are sold at lower prices and selling them in high-price countries: see Danzon P.M., (1998), *The economics of parallel trade*, Pharmacoeconomics, 13(3), 293-304.

16. The WTO is responsible for the implementation of the TRIPS agreements on intellectual property.

17. See e.g. Sykes A.O. (2002), *TRIPS, pharmaceuticals, developing countries, and the Doha solution*, Chi. J. Int'l L., 3, 47.

18. The proposal may be found at Documents Online Home page (wto.org) [available at https://docs.wto.org/dol2fe/Pages/FE_Search/FE_S_S005.aspx; latest access 30/11/2021].

19. These profits are far from negligible. Both BioNTech and Moderna, for instance, have reported profits of around €4 billion in the first semester of 2021: see BioNTech Announces Second Quarter 2021 Financial Results and Corporate Update | BioNTech [available at https://investors.biontech.de/news-releases/news-release-details/biontech-announces-second-quarter-2021-financial-results-and; latest access 30/11/2021] and Moderna Reports Second Quarter Fiscal Year 2021 Financial Results and Provides Business Updates | Moderna, Inc. (modernatx.com) [available at https://investors.modernatx.com/news-releases/news-release-details/moderna-reports-second-quarter-fiscal-year-2021-financial; latest access 14/11/2121].

20. On the optimal resolution to the innovation-diffusion trade-off see for instance Denicolò V. (2007), *Do patents over-compensate innovators?*, Economic Policy, 22(52), 680-729.

21. See Garde D., Saltzman J., *The story of mRNA: How a once-dismissed idea became a leading technology in the Covid vaccine race*, Boston Globe, November 10th, 2020 available at The story of mRNA: From a loose idea to a tool that may help curb Covid (statnews.com) [available at https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/; latest access 30/11/2021].

22. In fact, the role of big pharma is even more limited if one considers also the Indian, Russian, Iranian and Chinese vaccines, most of which have been developed by public research centers.

23. See Gentile I., Maraolo A.E., Buonomo A.R., Zappulo E., Borgia G. (2015), *The discovery of sofosbuvir: a revolution for therapy of chronic hepatitis C*, Expert opinion on drug discovery, 10(12), 1363-1377.

24. To mention just one such distortion, pharmaceutical companies' marketing expenditure compares to their expenditure on R&D: see, e.g., Gagnon M.A., Lexchin J. (2008), *The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States*, Plos medicine, 5(1), e1.

25. For an economic analysis of some of these conflicts of interests, see Henry E., Ottaviani M. (2019), *Research and the approval process: The organization of persuasion*, American Economic Review, 109(3), 911-55.

Beyond the Pandemic, Strategies For Vulnerable Women

Interventions in a Delhi Slum

by Amita Nigam Sahaya*

Abstract
The pandemic caused by Covid-19 has had a devastating effect on developing countries like India, as existing differences within the population in terms of access to resources and healthcare were greatly exacerbated with the economy going into a downward spiral and the healthcare system overwhelmed. The loss of incomes and joblessness further exposed the vulnerabilities of the urban poor particularly its women, as it triggered other inequities including gender related power equations. This paper trains its lens on an urban slum in Delhi as a microcosm, highlighting the challenges faced by the poor in metropolitan cities during the pandemic. It advocates the need to evolve strategies for the future by engendering a holistic interconnectedness between the different disciplines, ensuring that health issues are viewed not as separate silos but connected to the prisms of gender, autonomy and economics. It emphasizes the need to evolve not just immediate strategies to combat the impact of the pandemic but also design new methodologies that will address the gaps in health care systems that were exposed by the pandemic by introducing measures that will augment the existing infrastructure, while also intensifying the vaccination process. There is an urgent need to close the gender equality gap as a post-Covid world will need substantial increase in women's contribution to address the challenges faced across multiple fronts: economic, global warming; digital learning amongst others. This demands a paradigm shift in perspective and urgent actions to prevent future catastrophes.

1. Introduction

"In times of crisis, when resources are strained and institutional capacity is limited, women and girls face disproportionate impacts with far reaching consequences. Hard-fought gains for women's rights are also under threat"[1].

The substance of this statement was most devastatingly affirmed during the Covid-19 pandemic as it swept across the world causing unprecedented disruption and loss of lives, intersecting multiple areas such as health, economics, gender, education, and cultural and social life, with far reaching consequences. It's cataclysmic effect continues to this day, showcased as it is in decimated economies globally and the exacerbation of inequalities between the polarities of rich and the poor and between women and men.

India with the second largest population in the world and its large gap between the rich, the poor, the urban and the rural, in terms of access to resources and healthcare, has

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been critically impacted by the pandemic. The near total lockdown that followed the first outbreak devastated the economy with the closure of 49% of informal own units[2] leading to a possible increase in relative poverty rates from 22% to 36% among the informal workers[3] with the urban unemployment rate during the lockdown period jumping to nearly 24 percent in 2020. This particular section of the populace living precarious existences was further threatened, leading to a massive exodus of reverse migration from the urban to the rural. An approximate[4] 1.8 million were possibly repatriated as of May 2020; some sources estimate this number to have reached 25 million.

This Covid-19 wave 2020 was followed by a deadlier, more intense second wave in early 2021, led by the new mutant (B.1.617.2), resulting in a total of some 34518901[5] virus related cases in India and approximately 465911 deaths, though this is considered an underestimation.

Surveys focused on gender issues show that the pandemic has had a catastrophic impact on women and development and their economic and political participation with 118 women for every 100 men facing abject poverty[6] with women dropping significantly in the gender equality index[7].

The progress made on SDG5 in India too has been reversed[8] and there is a decline in female labour participation. Estimates[9] reveal that 19.3 percent of women with graduation and above qualifications are unemployed and were active job seekers during January-April 2021. The income of migrant workers' too has fallen by an average of 85 percent after returning to their rural areas of origin. Family savings have depleted, land and assets in some cases sold and the debt burden is weighing down women's lives. The second wave led to some unfortunate coinages that reflect the grim reality: Covid-Widows and Covid-Orphans.

2. Case Study of a Delhi Slum

To achieve a wider understanding of the impact of the pandemic on the economically vulnerable, particularly women, we focus on the microcosm of a slum / unauthorized colony in Delhi, as a reflection of the ground realities prevalent in this sprawling megalopolis. Slums / UCs grow in inverse proportion to the sweep of natural calamities, climate change, economic criticality, loss of livelihoods etc. that take place periodically in rural and semi urban parts of the country, forcing displacement and migration to larger towns and cites. An estimated 4 million people or about 25-30 per cent of Delhi's population of 19 million[10] lived in unauthorized colonies or UCs in 2013, which are marked by poor living conditions e.g. lack of piped water, overflowing garbage, open sewage etc.[11] The inhabitants of the area are mostly self–employed or work in private jobs or as contractual labour[12], Women are mostly engaged as part time domestic workers or work at the lower end of the occupational chain. They are low skilled, suffer from poor health; they also bear the brunt of household chores and lack agency and voice. The family incomes average around INR 10,000-25,000 monthly[13]. We need to appreciate however that these slums/UCs dwellers form the very backbones of metropolitan towns, providing the support systems and the ancillary services that oil the wheels of the administration and support the life styles of the middle and affluent classes living in the city centres[14].

3. Impact of Covid-19 on Health Issues

The post Covid-19 scenario has revealed women's physical and mental health as a major areas of concern. The overwhelming 2nd wave saw many primary care clinics shutting down and hospital facilities converted to Covid-19 wards to cope with the unprecedented number of patients. These measures drastically impacted regular health care, leaving the sickly or the terminally ill, particularly vulnerable[15].

Mental health related issues rarely talked about or recognized, are more prevalent in women than men as per studies[16]. They manifest as silent killers, spiking stress factors and causing various illnesses. Covid-19 has had a devastating impact on the Indian economy[17] causing one of the biggest contractions globally. This manifested in falling incomes and joblessness[18] and amplified mental health issues as mentioned earlier; increased[19] domestic violence, child abuse[20] an indicator being the huge rise in calls on Child helpline numbers[21]; aggravated depression and suicidal tendencies with a nearly 67 percent increase in reports of such incidents in the media.

4. Future Interventions and Strategies

The current scenario poses tremendous opportunities to review the situation and evolve strategies for the future by engendering a holistic interconnectedness between the different disciplines. Health cannot be viewed in an exclusive silo from the greater questions of gender, autonomy and economics; hence we need a paradigm shift in perspectives and methodology. Taking into account the shortage of medical personnel proportionate to the population[22] and the inadequacy of public health services in the country, a strategy would be to accord a greater role and recognition in medical care to frontline workers; such as the 2.3 million force of ASHA workers[23] Anganwadi[24] and AWMs (Auxiliary Nurse/ Midwives) who have tremendous outreach amongst the urban poor and rural women, as they are the first messengers for healthcare facilities. Recognizing the strength of their networks and outreach during the pandemic and its aftermath, both civil society and government bodies have used their services to reach out to vulnerable groups. They provided early health care and also played a vital role in spreading the message of vaccination and also implement its programs across the outlying regions of the country.

5. Vaccination – Innovative approaches

Vaccination has been the big driver to contain the virus and while the government has pursued the program aggressively with more than a billion doses given so far, yet there is a 20 percent gap in the vaccination ratio[25] between the sexes. This is caused by a variety of reasons that reflect the poor gender indices in the country e.g. lack of f access to mobiles, digital illiteracy, myths and fears and the low worth they ascribe to themselves. The vaccination drive has been supported by a two pronged strategy. government bodies have been administering free doses to the poor while the private medical facilities have a fixed price for the facility. In order to address some of the gaps in the system, civil society too joined the effort by conducting awareness campaigns to mitigate vax hesitancy and make the process more accessible, particularly in the urban slums, where the occupations of the women reveal their vulnerability (Figure 1).

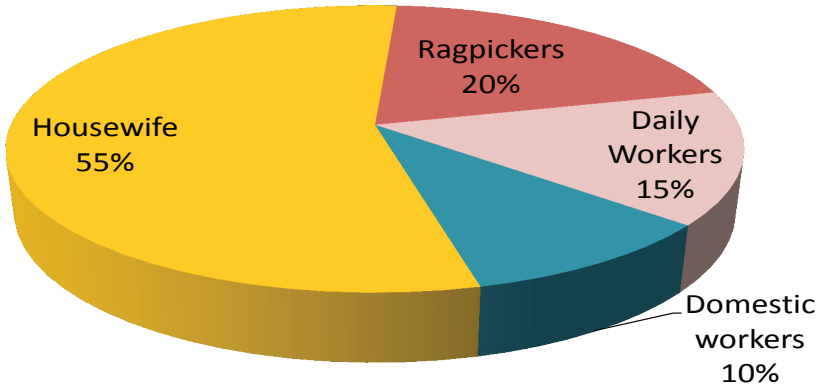

Fig. 1. Occupations of vaccinated women by percentage.

6. The Gender Dimension – Closing the Equality Gap

The post-Covid world needs a substantial increase in the contribution from women – the one half of the population – to address the challenges it faces across multiple fronts: economic, global warming; digital disruption, inclusive growth, workforce and skills among others. This can be enabled only by closing the gender equality gap and empowering women. It involves changing their perceptions about themselves, to have the agency to have access to resources: material, human and social and to utilize them, and to understand and recognize injustice both institutionalized and sporadic[26]. Empowerment is inextricably linked to economic agency which is fundamental to poverty reduction and food security, lasting, inclusive and sustainable economic growth.

The development effect of putting more money in the hands of women makes imminent sense as they spend a greater portion of their incomes on their families, hence Increasing women's incomes and their control over family spending will have a domino effect on improvements in child nutrition, health, education and work, thereby breaking the cycle of intergenerational poverty. Higher levels of gender equality also generates lowered poverty and food insecurity in the general population, higher standing in the Human Development Index, and less environmental degradation[27].

Given this scenario, the falling rate of female labour force participation in India at 31 percent including both rural and urban[28] is of deep concern. Various socio-cultural, economic factors lie behind this reality, which demands a substantive and well structured redress from government agencies, private sector and civil society, that must be backed by political will.

A major step in this direction would be to substantially increase women's digital inclusion as a key gateway to financial services and opportunities for income generation, besides education, information and every form of learning[29] The post-Covid world has witnessed an exponential rise in the usage of technology and digitalization and women at current internet accessibility, lagging behind men by nearly 135 million in India, must be granted incentives to close the gender gap. To this effect various government and NGOs have started Computer Classes for girls and women in the slum area. Similarly[30] skill training and up skilling is a vital part of improving women's job possibilities and liberating them from the lowest end of the occupational hierarchy.

Increased political participation at the grassroots and higher levels is a vital element to give women a voice in governance. While twenty State governments have reserved 50 percentage of seats for women at the local level, the highest political body the Lok Sabha has a mere 14 percent of women candidates.

7. Conclusion

The post-Covid reality demands a paradigm shift in perspectives and the way we shape our future – for ourselves and for the generations to come. The extraordinary challenges, death and devastation caused by the pandemic leaves us lessons that cannot and should not be ignored. Abjuring the irresponsible exploitation of resources and bridging the silos dividing communities, the sexes and the rich and poor is urgently needed as an interconnected world leaves us no room for complacency. The next disaster is waiting in the wings. This perhaps is the pandemic's most powerful message.

Notes

1. *Explainer How Covid-19 Impacts Women & Girls* [Internet] Un Women [updated 17 March 2021] [available at https://interactive.unwomen.org/multimedia/explainer/covid19/en/].

2. *Annual Report 2020 Going Beyond Crisil* [Internet] [December 2020] [available at https://www.crisil.com/en/home/investors/financial-information/annual-report-info-2020.html].

3. *Covid-19 and the World of Work. ILO Monitor: Seventh edition* [Internet] Updated estimates and analysis [25 January 2021] [available at https://www.ilo.org/wcmsp5/groups/public/@dgreports/@dcomm/documents/briefingnote/wcms_767028.pdf].

4. *Reverse migration to rural areas of origin in the context of the Covid-19 pandemic, Food and Agricultural Organization of the United Nations* [Internet] [12 May 2021] [available at http://www.fao.org/3/cb4712en/cb4712en.pdf].

5. *India Fights Corona Covid-19 Mygov* [Internet] [22 November2021] [available at https://www.mygov.in/covid-19/).

6. *UN Women Highlights from 2020-2021*, Un Women [Internet] [2021] [available at https://www.unwomen.org/en/digital-library/annual-report].

7. *Global Gender Gap Report 2021*, World Economic Forum [Internet] [31 March 2021] [available at https://www.weforum.org/reports/ab6795a1-960c-42b2-b3d5-587eccda6023. Available at https://www.orfonline.org/expert-speak/covid19-gendered-impact/].

8. *Sangita Dutta Gupta & Susmita Chatterjee Covid-19 and its gendered impact*, Observer Research Foundation [Internet] [December 23 2020].

9. Mahesh V., *The Jobs Bloodbath of April 2020*, Centre for Monitoring Indian Economy [Internet] [5 May 2020] [available at https://www.cmie.com/kommon/bin/sr.php?kall=warticle&dt=2020-05-05%2008:22:21&msec=776].

10. *2011 Census data*, Office of the Registrar General & Census Commissioner, India Ministry of Home Affairs, Government of India [Internet] [available at https://censusindia.gov.in/2011-common/censusdata2011.html].

11. Prerna Prabhakar National Council of Applied Economic Research (NCAER) Aman Agarwal Gokhale Institute of Politics and Economics Divy Rangan Ashoka University; Urban Policy Failure in Delhi: A Case of Unauthorised Colonies; Researchgate [Internet] [May2020] [available at https://www.researchgate.net/publication/341592888_Urban_Policy_Failure_in_Delhi_A_Case_of_Unauthorised_Colonies].

12. *Sugata Bag, Urban Female Labor Force Participation and Its Correlates: A Comparative Study of Slum-Dwellers and Their Urban Counterparts of Three Metro Cities in India*, Delhi School of Economics, [Internet] [posted 6 April 2020] [available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3552663].

13. 125-312 euros at current rates of exchange.

14. Vivek G., Shubham Y., Shraddha G., *694 Impact of Covid-19 in India's Urban Slum and Informal Settlement*. International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056 Volume: 07 Issue: 07 | [July 2020] [available at www.irjet.net p-ISSN: 2395-0072 © 2020, IRJET, Page].

15. Toteja G.S., Singh P., Dhillon B.S., Saxena B.N., Ahmed F.U., Lt. Singh R.P., Prakash B., Vijayaraghavan K., Singh Y., Rauf A., Sarma U.C., Gandhi S., Behl L., Mukherjee K., Swami S.S., Meru V., Chandra P., Chandrawati, Mohan U., *Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India*, Sage Journals [Internet] [available from https://journals.sagepub.com/doi/pdf/10.1177/156482650602700405].

16. Afridi F., Dhillon A., Roy S., *The Impact of Covid-19 on Livelihoods and Mental Health among the Urban Poor in India Policy brief IND-20093* [Internet] [March 2021] [available from https://www.theigc.org/wp-content/uploads/2021/03/Afridi-et-al-2021-Policy-brief-1.pdf].

17. Dhingra S., Ghatak M., *How has Covid-19 Affected India's Economy*, Economics Observatory [Internet] [30 June 2021] [available at https://www.economicsobservatory.com/how-has-covid-19-affected-indias-economy].

18. *State of Working India 2021; Centre for Sustainable Employment*, Azim Premji University [Internet] [released 5 May 2021] [available at https://cse.azimpremjiuniversity.edu.in/state-of-working-india/swi-2021/].

19. Chandra J., *National Commission for Women records sharp spike in domestic violence amid lockdown*, The Hindu [Internet] [June 15 2020] [available at https://www.thehindu.com/news/national/ncw-records-sharp-spike-in-domestic-violence-amid-lockdown/article31835105.ece].

20. Hitanku D. Priyank Y., *Psycho-social impact of Covid-19 pandemic on children in India: The reality*, US National Library of Medicine National Institutes of Health; [Internet] [Published online 2020 Aug 10] [available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833725/].

21 *Increased number of suicide cases reported during Covid second wave*, The New Indian Express [Internet] [Last Updated: 09th September 2021] [available at https://www.newindianexpress.com/cities/delhi/2021/sep/09/increased-number-of-suicide-cases-reported-during-covid-second-wave-2356346.html].

22. Every allopathic doctor in India caters to at least 1,511 people, much higher than the World Health Organization's norm of one doctor for every 1,000 people. The shortage of trained nurses is even more dire, with a nurse-to-population ratio of 1:670 against the WHO norm of 1:300.

23. Accredited Social Health Activist (ASHA) is a trained female community health activist. Selected from the community itself and accountable to it, the ASHA will be trained to work as an interface between the community and the public health system.

24. Anganwadi workers: The Anganwadi worker is a community based front line worker of the ICDS (Integrated Child Development Services) Programme. She plays a crucial role in promoting child growth and development. She is also an agent of social change, mobilizing community support for better care of young children.

25. Mishra M., Jain R., *Women Falling Behind in India's Covid-19 Vaccination Drive*, The Wire [Internet] [June 8, 2020] [available at https://thewire.in/gender/women-falling-behind-in-indias-covid-19-vaccination-drive].

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27. Parsuraman S., Somaiya M., *Economic Empowerment of Women Promoting Skills Development in Slum Areas Report*, The EEWSD Study sanctioned by the Ministry of Women and Child Development implemented by Tata Institute of Social Sciences (TISS), Mumbai. [December 2016].

28. Urmila, Chatterjee, Rinku, Murgai, Martin, Rama, *Job Opportunities along the Rural-Urban Gradation and Female Labor Force Participation in India*, Policy Research Working Paper, World Bank Group, Poverty Global Practice Group & Office of the Chief Economist South Asia Region [published September 2015].

29. Sahaya A., *Women's Working World – A Mirror to Their World*, Lambert Academic Publishing, 2019.

30. *National Skills Network*, Ministry of Skill Development and Entrepreneurship (MSDE) Government of India [Internet] [March 9 2019] [available at https://www.nationalskillsnetwork.in/skill-india-women-initiatives/].

The transformation of the hospital during the second wave of Covid

Lesson learnt. The experience of Poliambulanza Hospital in Brescia (Italy)

by Renzo Rozzini, Letizia Bazoli, Erika Tonoli, Silvia Singia, Angelo Meloni*

Abstract
The paper describes how the mandatory subversion of the hospital during the Covid second wave (arrived in November 2020), thanks to the experience gained in the first wave, prompted toward a more prepared and ready system with a specific organized response, i.e. a modulated reception modality activated for the different types of patients, a close monitoring of the most serious, an intensive care for patients with more primary needs, and a interdisciplinarity and relationship with the community care once the hospital procedure is finished. A legacy from that experience could be useful in the next years in order to make hospitals more efficient to care all patients, not only the infective ones.

1. Introduction

The Covid-19 pandemic has had a disruptive effect on the entire healthcare landscape and therefore also on the hospital system, causing a reconsideration of the way services are offered which in the future will significantly affect the healthcare offer.

The first wave hit a part of our region, and Brescia in particular, with unexpected brutality. Starting from the third week of February, after the identification of the first Coronavirus outbreaks (in the province of Lodi), the wave of the epidemic reached Brescia, with access to hospital emergency rooms which, from 23 February 2020 onwards, recorded a progressive impressive intensification.

In our hospital (600 beds, Fondazione Poliambulanza – Istituto Ospedaliero, Brescia) in just under two months more than 2,200 patients were received and treated, 1450 of whom were hospitalized. A total of 186 patients were hospitalized in intensive care unit (during the most critical moment 430 Covid patients were hospitalized and up to 78 beds were set up and made available, compared to 21 in the ordinary times).

The hospital was completely transformed, with a revision of

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almost all operating paradigms: the birth point kept active and only 3 (out of 13) operating rooms, for emergency interventions and oncological emergencies; all elective admissions and all outpatient activities were blocked, strengthened the staff of the intensity (all the strengths and skills of resuscitators, anesthetists and operating room nurses have been destined for Covid-19 patients); specific training courses were organized for the doctors of different disciplines converted to Covid patient care (to support back-up in the departments and emergency room), 9 departments were converted and equipped for this function; over a hundred professionals were recruited from outside.

The hospital has gone from a daily consumption in the ordinary situation of about 600 liters to 12,000 liters at the peak of the crisis (this involved the acquisition of additional tanks, the construction of new distribution and supply systems).

The function of bed manager has been established: three operators always active controlling the beds' occupation (of which, at the moment of maximum occupancy, 360 with ventilatory assistance at various levels of intensity) according to patients clinical and nursing care needs[1].

In summary, in a few days, forced by the overwhelming pandemic pressure, the hospital had to transform from a multi-specialty hospital to a Covid hospital and little time to work out a more appropriate process of care was left[2].

2. The second wave

The second wave, which arrived in November 2020, again subverted the characteristics of the hospital, but on this occasion, thanks to the experience gained in the first wave, it was addressed by a more prepared and ready system with a specific organized response.

Strengthened by the awareness that the organization, rather than the clinic (lacking now as then a specific effective treatment), would have produced the most favorable outcomes for patients, a modulated reception modality was immediately activated for the different types of patients: close monitoring of the most serious, intensive care in patients with more primary needs, interdisciplinarity and relationship with the community care for patients with greater home care needs to be satisfied once the hospital procedure is finished.

Even before Covid, our hospital, like many of the advanced hospital organizations, had started to shape the clinical paths accordingly to a multidisciplinary and transversal vision of care and applying models able to efficiently and effectively support processes for different cure needs (i.e. Progressive Patient Care & Patient Centered Care – PCC)[3].

The second wave of the pandemic has accelerated the ongoing change. This transformation, according to the creation of homogeneous paths by type of patients of different clinical severity and with different care complexity (model for intensity of care), was the intuitive organizational choice. This model was realized creating and assigning to different macro-areas of care, with specific and appropriate skills, patients with different disease severities and at different times regarding their disease trajectory.

3. Actions-Filter area (selection processes)

The first action taken was the creation of a high turnover area ("filter area") reserved for

Tab. 1. Prognostic Risk Index of in-hospital mortality.

Age	score	CMB	score	RR	score	P/F	score	Creat	score	Ptls	score
< 62	1	≤1	1	≤20	1	> 300	1	<.83	1	> 212	1
62-74	2	2-3	2	21-24	2	236-299	2	0.83-1.12	2	156-211	2
≥ 75	3	≥4	3	≥ 25	3	< 236	3	≥ 1.13	3	< 156	3

CMB: number of comorbidities; RR: respiratory rate per minute; P/F: PaO2/Fio2 ratio; Creat: serum creatinine; PLTS: platelets number. Prognostic risk is calculated by adding up the scores: (Low = ≤ 10 Intermediate = 11-13 High = ≥ 14 tot. (Fumagalli et al, BMJ, 2020)

Tab. 2. "Silver code" to evaluate the pre-hospital clinical frailty.

Have you had a PS / DEA login in the past six months?
Have you been hospitalized in the past six months?
Do you need someone to prepare or administer medicines?
Do you need a person to help you get out of bed or walk?
Is the patient in charge of home care services (day center, sheltered home, Nh)?

patients from the ER with a definite indication for hospitalization and waiting for a swab report.

In the filter area patients were stratified according to their clinical severity due to the Sars-Cov2 infection (by the Prognostic Risk Index of in-hospital mortality; Table 1), to their pre-existing medical status (i.e. comorbidity, disability), and to non-biomedical areas that could have influenced both the prognosis (aggravating factors) and discharge for each patient (The Silver Code, Table 2)[4].

The integration of the clinical characteristics with the comorbidities, functional status, and extra clinical ones (i.e. non biomedical factors) allowed the definition of:

- the patient's health status (weight of the severity of the index pathology with respect to comorbidities or vice versa);
- the goal of care (lifesaving or maximization of palliative care and end-of-life comfort);
- the level of intensity of the treatments to be activated: intensive, global-comprehensive, palliative and comfort therapy, and basic.

The definition of patients' characteristics and the treatment's objectives allow the bed manager to manage the first allocation of the patients in a flexible way in the macro-areas designated ("ward triage").

4. The macro-areas of hospitalization

Specifically, 4 sectors (macro-areas) have been identified:

- a high-intensity sector called 2P Tower (it receives patients who require any type of therapy, potential candidates for transfer to ICU: in this sector, patients on non-invasive ventilation, patients with high-flow O2 delivery and Venturi Mask (VM) are admitted; this sector also receives patients who require palliative therapy, both for the management of NIV and in the terminality phase);
- a medium-intensity sector called 4P Tower (it accommodates patients with severe pneumonia or ARDS with no maximum need for O2 supply with MV);
- two low-intensity sectors respectively named 3P east and 4P tower (welcoming stable patients, with O2 delivery in CN, or clinically cured patients waiting to be transferred to specific post-acute settings (post-Covid settings) due to their inability to return home for environmental problems or for the worsening of the functional state following the Sars-CoV-2 infection or the hospitalization).

Surgical patients with incidental Sars-CoV-2 infection were admitted to both the high- and medium-intensity sector.

The structure of the wards was naturally flexible, adapting to changes in both the state of health of patients and the epidemiology of demand (and the skills of the available assistance staff).

Obviously even the "No Covid areas", although significantly reduced, had to reorganize themselves by adopting, to maximize their efficiency, the multi-specialty care intensity model.

5. The assistance staff

The adopted model required the placement of staff in the various settings by virtue of the skills possessed.

As far as doctors are concerned, senior doctors with clinical skills and experience gained in the field of intensity were identified, were dedicated to lead the high and medium intensity sectors, and junior doctors (capable, due to physical and mental energy, of maintaining the will and ability to continue working even in the most stressful and difficult conditions due to the mix of clinical and non-clinical aspects) were dedicated to lead the low intensity sectors with high discharge rates. The doctors of the other specialties performed a support function.

A conversion of Nurses and Social Health Operators of the surgical departments in Covid nurses was required; the presence of the staff was organized on the basis of their competence in the intensity of care and "measuring" their presence according to different "nurse to patient ratio" (Department of Health, UK, 2013).

Skills and staff numbers were thus the organizational drivers, which combined with the clinical complexity of the patients made it possible to organize the intensity of care (Table 3).

6. After covid: lesson learnt

Organization legacy built during the pandemic after the last covid patient was discharged:

- The function of bed manager has been definitively established; one operator is now

Tab. 3. Characteristics of the Covid sectors and relative "dose-assistance" ratios during the second wave.

Sector	Intensity	beds	Patients / nurses	Patients / Inf & OSS	Skill mix nurses
2P Tower	High	40	9,5	6,8	71,6%
4P Tower	Medium	32	10,7	6,7	79,0%
4P Est	Low	24	9,5	7,5	79,2%
5P Tower	Low	40	10,9	8,6	79,5%

active 24 hours a day (with control of the beds' occupation), he responds to the requests of the emergency room concerning the placement of the patients according to their medical or surgical and nursing care needs.
- Multidimensional evaluation for all patients, detecting clinical severity, biomedical and functional burden, and non-biomedical needs (all of them able to influence prognosis and discharge feasibility) is adopted and performed in ER; now it is the tool used by the bed manager to allocate patients in the different wards.
- In surgical department the model for intensity of care (homogeneous paths by type of patients of different clinical severity and with different care complexity), was realized.
- Nurse to patient standard were revised and different "care dose" is now the rule adopted in all departments.

7. Conclusions

The Covid-19 crisis has imposed at the hospital level a reflection on the paths to be taken not only to redeem the many deaths, but to produce concrete and structural acts of recognition and protection for the entire population who will require hospital care[5].

To avoid being drained into the cynicism that the pandemic crisis will bring, hospitals can make pragmatic choices that favor the quality of care rather than the repetition of what is already known. Some suggestions learnt:

- *Flexibility*. What happened for the emergency should have a follow-up in the ordinary. Ability to quickly change function to beds according to the required needs. This happened for emergency reasons. The design of new hospitals should consider this aspect, partly already achieved with the new hospitals designed according to the "intensity of care". We should think of medical areas no longer separated by walls (and not only structural), but large areas where patients can access regardless of their acute clinical picture (special situations such as acute STEMI heart attack, stroke, for which to prepare areas flexible equipped).
- *Co-management*. During the pandemic infectious disease specialists, pulmonologists, internists and specialists from other disciplines each

intervened on the individual patient according to his skills, going beyond what until yesterday was a single simple consultation. Co-management need to be an ordinary practice.

– *Technology*. During the pandemic we all realized how necessary it was to have efficient, easily maneuverable, not obsolete machinery. Not only ventilators but also ultrasound (vascular, cardiological, thoracic, abdominal) has facilitated diagnostics and consequently treatment. In large medical areas, at least 20-30% of "High Care" beds must be present, ie beds equipped with technology for monitoring vital parameters with relative observation and control unit.
– *The competence*. Specific skills will be needed but also general skills in all hospital wards. There will be an increasing need for doctors who are able to have an overall view of the problems of each individual patient, to distinguish their priorities, to coordinate their entire assistance and care during hospitalization.
– *The structural organization*. Even before the pandemic, the problem of the lack of adequate facilities for patients discharged from an acute care hospital but not yet in conditions capable of being managed at home was relevant. It is necessary to invest in "intermediate care" by creating ad hoc structures or by converting abandoned structures or those destined for other uses to this function.
– *The relationship with the territory*. The hospital must become an open structure as much as possible. The relationship with local doctors and, where present, with the local nurse must become a mandatory and possible path also with IT means.

The achievement of these goals will be possible if the rigid constraints overcome by the imperative necessity (and enthusiasm) of the first wave, but evident and limiting in the second, are overcome with regulatory, as well as intellectual flexibility, which allows operationally adapting the hospital's responses to needs of the patient.

Finally, organized systems require "discrete" information (objective assessment), which, while not representing indisputable references, allows more appropriate responses to the individual patient, and a more equitable distribution of available resources. However, it will be important to avoid the danger that the thought underlying the organization (the technology and technicality) can become dominant, overwhelming the ideal inspiration of the hospital which, instead, must take advantage of the organization and technology, but refuse to be dominated by them.

Box 1.

Framework: Hospital organization changes during the second Covid pandemic and what's is left at its end are described.
Approach: model of care was guided by a modulated reception modality for the different patients, i.e. close monitoring of the most serious, intensive care in patients with more primary needs, interdisciplinarity and relationship with the community care for those with greater home care needs to be satisfied once the hospital procedure is finished.
Setting: Poliambulanza Hospital (Fondazione Poliambulanza - Istituto Ospedaliero, Brescia) 600 multi-speciality beds.
Relevant changes: different sectors of care were realized; a filter area for the selection processes according to patient's clinical severity, pre-existing medical status, and non-biomedical areas potentially influencing prognosis and discharge. Three macro-areas of care: a high-intensity sector, a medium-intensity sector, and two low-intensity sectors
The assistance staff: Medical senior leaders with clinical skills and experience gained in the field of intensity were dedicated to the high and medium intensity sectors, and junior leaders to low intensity sectors with high discharge rates. Conversion of nurses and social health operators of the surgical departments in Covid nurses has been done on the basis of their competence in the intensity of care and "measuring" their presence according to different "nurse to patient ratio".
Lessons learnt: Flexibility (ability to quickly change function to beds according to the required needs), co-management (specialists from different disciplines intervening according to his skills), technology (need of efficient, easily maneuverable, not obsolete machinery), the competence (specific skills but also general skills will be needed in all hospital wards); structural organization (need of adequate facilities for patients discharged from an acute care hospital; the relationship with the territory (The relationship with local doctors and, where present, with the local nurse must become a mandatory and possible path also with IT means).

Notes

1. Triboldi A., *La risposta della comunità all'emergenza sanitaria*, in *Le Cento giornate di Brescia*, Simeone D., Bianchetti A., Rozzini R., Schole, Brescia 2021.

2. Rozzini R., Bianchetti A., *Covid Towers: low- and medium-intensity care for patients not in the ICU.CMAJ*, 2020; 192: E463-E464-Department of Health. Hard Truths, The Journey to Putting Patients First, Department of Health, London 2013.

3. Guarinoni M.G., Motta P.C., Petrucci C., Lancia L., *Progressive Patient Care e organizzazione ospedaliera per intensità di cure: revisione narrativa della letteratura*, Professioni Infermieristiche, 2014, 66: 205-14.

4. Fumagalli C., Rozzini R., Vannini M. (*et al.*), *Clinical risk score to predict in-hospital mortality in Covid-19 patients: a retrospective cohort study*, BMJ Open, 2020; 10:e040729.

5. Rozzini R., *The Covid Grim Reaper*, J Am Med Dir Assoc. 2020; 21:994.

Cardiovascular prevention in the twenties of the 21st century

Lessons learned and future directions

by Diego Vanuzzo, Simona Giampaoli*

Abstract

The bases of cardiovascular prevention are rooted in cardiovascular epidemiology and evidence-based medicine since 1961, when investigators in the Framingham Heart Study found that healthy subjects with "risk factors" such as hypertension, hypercholesterolemia, and with smoking habit had a greater probability to suffer from coronary heart disease. Subsequently other risk factors were identified, e.g. diabetes, and it was demonstrated that they predicted also other atherosclerotic diseases, e.g. stroke and peripheral artery disease. There was evidence that lifestyles were responsible for high levels of these risk factors and many other concepts have evolved in cardiovascular prevention, from the notion of global risk, to the Rose's proposal of the two complementary approaches of "population strategy" and of "high risk" individual strategy, and to the formulation of "primordial prevention" since pregnancy and childhood to prevent the development of risk factors. Many studies were performed in order to evaluate the effects of risk reduction, and the major lesson learned about cardiovascular prevention demonstrate that primary prevention driven by secular trends in lifestyle and clinical risk factors, played a major role in the cardiovascular mortality decline in many populations. Future directions in this field include genetic research and development of polygenic scores which can be used as an additional tool to support therapeutic decisions in people at intermediate risk, research on biomarkers, in particular of inflammation, on imaging both ultrasonographic and radiological and on their integration, favoured by computer applications defined "machine learning". Finally, metabolic phenotypes and other artificial intelligence approaches are being studied to obtain "precision prevention".

"It is better to be healthy than ill or dead. That is the beginning and the end of the only real argument for preventive medicine. It is sufficient"[1]. This concise and clear statement of Geoffrey Rose, one of the pioneers of cardiovascular epidemiology and prevention in the last part of the 20th century may seem somewhat ironical during the Covid-19 pandemic, when an effective vaccination campaign[2] is counteracted by a significant vaccine hesitancy[3]. But it underlines the need of an effective prevention in a setting which was defined the "perfect storm of rising chronic diseases and public health failures fuelling Covid-19 pandemic"[3] by a Lancet press release illustrating the last reports of the Global Burden of Disease Study (GBD)[4,5] updated to 2019. According

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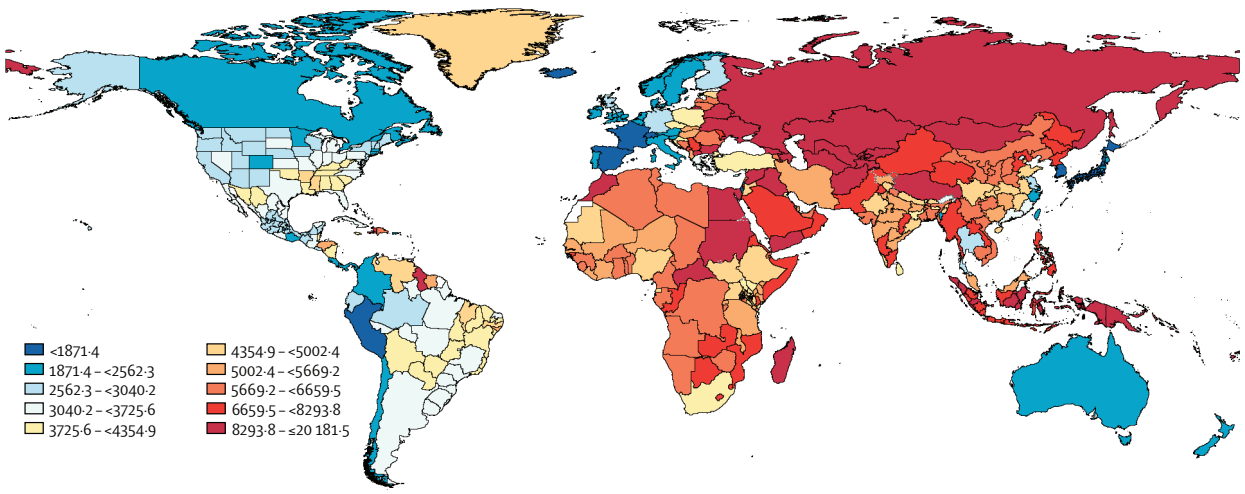


Fig. 1. Age-standardised DALY rates (per 100000) by location, both sexes combined, 2019 [derived from http://www.healthdata.org/results/gbd_summaries/2019/cardiovascular-diseases-level-2-cause].

to those GBD reports, leading causes of DALYs or health loss globally for both sexes combined, all ages, in 2019: were, after the first, neonatal disorders, driven by the DALY definition, Ischaemic heart disease (2nd) and Stroke (3rd). Risks associated with the highest number of deaths worldwide, in 2019 were:

- High systolic blood pressure (10.8 million deaths);
- Tobacco (8.71 million deaths);
- Dietary risks (e.g., low fruit, high salt) (7.94 million deaths);
- Air pollution (6.67 million deaths);
- High fasting plasma glucose (6.50 million deaths);
- High body-mass index (5.02 million deaths);
- High LDL cholesterol (4.40 million deaths);
- Kidney dysfunction (3.16 million deaths);
- Child and maternal malnutrition (2.94 million deaths);
- Alcohol use (2.44 million deaths).

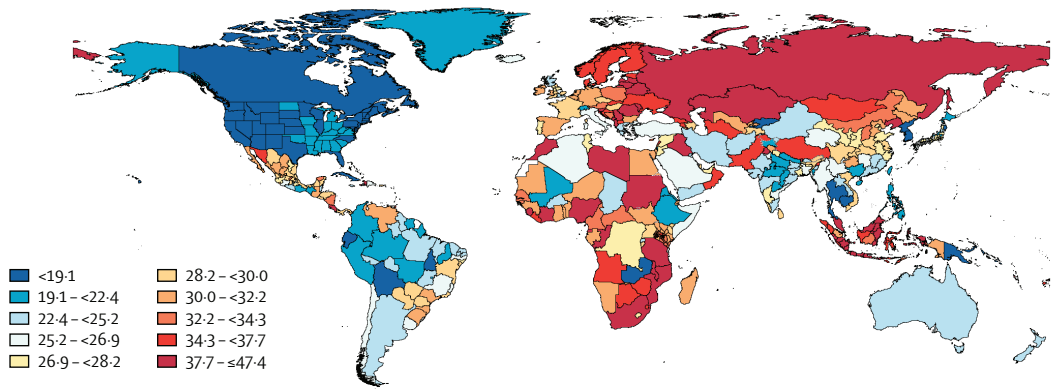
All those facts underline the need of an effective cardiovascular prevention all over the world, together with the efforts to curb the Covid-19 pandemic and to counteract the climate change. Certainly, prevention and surveillance policies should adapt to the different impact of cardiovascular diseases and their risk factors in the various countries (Figure 1-2)[5,6].

In this paper we will consider the results achieved and the possible future scenarios of cardiovascular prevention, which may be defined, adapting John Last's words[7], as a coordinated set of actions, at community and individual level, aimed at eradicating, eliminating or minimizing the impact of cardiovascular diseases (CVD) and their related disability.

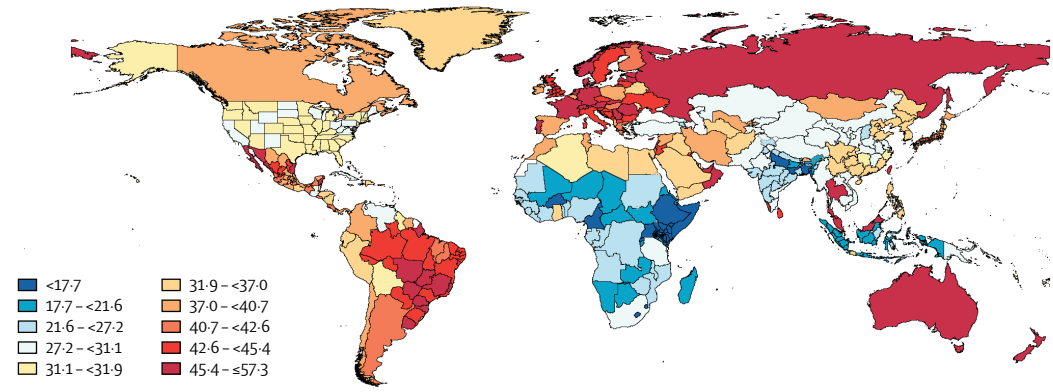
1. Results achieved by cardiovascular prevention

The bases of cardiovascular prevention are rooted in cardiovascular epidemiology and evidence-based medicine since 1961, when investigators in the Framingham Heart Study had shown that overtly healthy subjects with

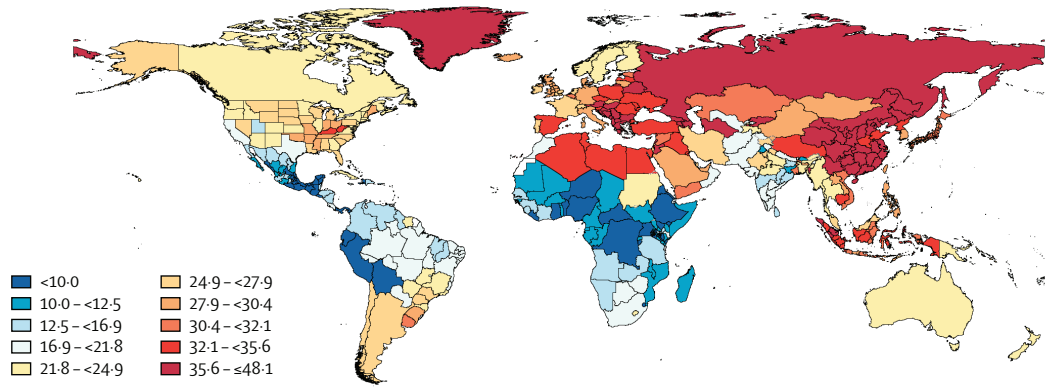
HIGH BLOOD PRESSURE



HIGH LDL CHOLESTEROL



TOBACCO



SEV = summary exposure values, a measure of exposure to a risk factor normalized on a scale of 0 to 100 to make comparisons possible between dichotomous, polytomous, and continuous risks by country or territory, and selected subnational locations.

Fig. 2. Age-standardised all-cause SEV by location, both sexes combined, 2019 [derived from http://www.healthdata.org/results/gbd_summaries/2019].

hypertension, hypercholesterolemia, and with smoking habit were at higher risk of developing an acute myocardial infarction[8]; they coined the term 'coronary risk factors'[9]. There is evidence that lifestyles are responsible of levels of the risk factors[10,11].
In the following years many other concepts have evolved in CVD prevention, from the predictive value of coronary risk factors for other atherosclerotic diseases, like stroke and peripheral artery disease[12] so they are termed "cardiovascular risk factors", and from the notion of global CVD risk, to the Rose's proposal[1,13] of the two complementary approaches of "population strategy" (i.e. shifting adverse population risk distribution toward lower levels) and of "high risk" individual strategy, and to the Tom Strasser's formulation of "primordial prevention" since pregnancy and childhood to prevent the development of risk factors[14].
More recently the attention was paid to the possible positive long-term consequences of favourable risk profile and to the issue of maintaining a low cardiovascular risk at all ages proposed by Jeremiah Stamler *et al.*[15]

1.1. *Global CVD Risk Estimation and the low-risk approach*

The global absolute CVD risk represents the likelihood of developing the disease over the following years, provided that the value of several risk factors is known. It is estimated through a risk equation using base-line risk factors and morbidity and mortality data of general population free of CVD at baseline and followed up in longitudinal studies.
The risk equation includes: mean risk factors values of the population, risk coefficients, which attribute an etiological weight to single factors[16], and survival probability. These elements change according to different populations, particularly when different cultures or generational cohorts are compared. The identification of CVD risk has become one of the main targets of primary prevention and the first step to reduce modifiable risk factors, from lifestyle changes to pharmacological treatments.
Many tools were developed over time, including also the analysis of competing risks; the most recent ones are the SCORE2[17] and SCORE2-OP (older persons)[18] in Europe, and the Pooled Cohort risk equations in the US, developed by a working group as part of the ACC/AHA 2013 Guideline on the Assessment of Cardiovascular Risk[19] in the U.S. In Italy the Progetto CUORE[20,21] allowed the development of a risk score and risk charts for men and women separately, considering the first major coronary or cerebrovascular event as the endpoint[21] including age, systolic blood pressure, total cholesterol, HDL-cholesterol, smoking habit, diabetes, and hypertension treatment. The Progetto CUORE also allowed the researchers to evaluate the fate of the so-called favourable risk profile or "low risk" individuals[22,23]. This definition included persons with all the following characteristics: total cholesterol < 5.17 mmol/l (< 200 mg/dl), systolic blood pressure (SBP) ≤ 120mmHg, diastolic blood pressure (DBP) ≤ 80 mmHg, no antihypertensive medication, body mass index (BMI) < 25.0 kg/m^2, no diabetes, no smoking; they were compared with individuals at "unfavourable but not high-risk" and at "high risk" – see the original articles[22,23] for definitions. Low risk individuals were only 3% at baseline, and they had virtually no coronary heart disease (CHD) and cerebrovascular diseases in the

following ten years. The rates for unfavourable but not high-risk individuals (17% of the CUORE cohort) and high risk individuals (80%) were higher and with a graded increase to one, two and three or more risk factors.

1.2. *Epidemiological evidence of cardiovascular prevention effectiveness*

While randomized double blind clinical trials form the basis of treatment evidence in high risk individuals, intervention programs at community level are much more difficult to perform and often with scarce results, as also recent experiences demonstrate[24,25], because of the influence of strong secular trends. Therefore it is better to rely on large standardized observational studies to evaluate prevention effectiveness. This is the case of the MONICA Study[26,29], more consistent than other modelling studies. According to MONICA data, regarding 36 populations in 21 countries of four continents, totalling 15 million people, in men CHD mortality rates decreased in 25 populations and increased in 11 populations; in women CHD mortality rates decreased in 22 populations and increased in 13 populations. In percentage terms, decrease in mortality rates in the MONICA data was less than that recorded in official mortality rates based on death certificate data. The MONICA Project demonstrated the substantial contribution of both decreased incidence and increased survival as well as the changes in the prevalence of risk factors to the declining trend of mortality: one third of the decline in mortality was explained by changes in case fatality rates related to advancements in coronary care, two thirds by declining incidence in coronary events as partly explained by the reduction of classical risk factors.

In conclusion the lesson learned about CVD prevention demonstrate, in the continuum from primordial prevention to secondary prevention and rehabilitation, that primary CVD prevention driven by secular trends in lifestyle and clinical risk factors, played a major role in the CVD mortality decline in many populations, but its potential is much wider, aiming at reducing also the non-fatal CVD cases, other non-communicable diseases, premature and late disability, ensuring therefore a healthy aging to the majority of people.

2. Future directions in cardiovascular prevention

The results of the GBD study[4,5] regarding 2019 indicate that there has been a substantial slowdown in the rate of decline of cardiovascular-disease (CVD) mortality in many high income countries in recent years: this was most apparent at ages 35–74 years, where CVD-mortality rates have increased in the USA (males and females) and Canada (females); high and increasing obesity, among other risk factors, jeopardize further CVD-mortality declines in many countries. Moreover the Covid-19 pandemic has a significant death toll worldwide[29] and increases the burden of CVD[30]. Therefore there is a real need for innovative ways to create new approaches to CVD prevention, both in the realm of individual precision medicine and in the one of community intervention.

2.1. *Precision CVD prevention from the polygenic scores to biomarkers, imaging techniques and artificial intelligence applications*

A familial pattern in the risk of CHD was found in large studies involving twins and prospective cohorts[31,32]. Since 2007,

genome-wide association analyses have identified more than 50 independent loci associated with the risk of CHD[33]. These risk alleles, when aggregated into a polygenic risk score, are predictive of incident coronary events and provide a continuous and quantitative measure of genetic susceptibility[33], which can identify subjects with a risk equivalent to individuals with familial hypercholesterolemia, but without an elevated LDL cholesterol[34]. A recent study confirmed that people with intermediate LDL levels (e.g. between 130 and 160 mg/dL), but with a high polygenic score, have the same risk as those with severe hypercholesterolemia[35]. The polygenic score can be used as an additional tool to support therapeutic decisions in people at intermediate risk, often difficult to reclassify with the other tools available[36]. Furthermore, statins and PCSK9 inhibitors were more effective in people with high polygenic scores, with higher benefits[37, 38].

Other research on coronary risk stratification or reclassification has focused, in addition to genetics and its scores, on biomarkers, in particular of inflammation[39], on imaging both ultrasonographic[40, 41] and radiological[42] and on their integration[43], favoured by computer applications defined "machine learning"[44] an approach based on computer systems capable of learning and adapting without following explicit instructions, using algorithms and statistical models to analyse and drawing inferences from patterns in the data. Finally, "metabotypes" metabolic phenotypes are being studied to obtain "precision prevention", especially from the food point of view[45].

These scenarios are certainly interesting but two problems immediately emerge:

- once the best tools for "precision prevention" have been identified, their cost and their real applicability at the population level, in particular in primary prevention, must be assessed[46];
- considering the population, the community context emerges also for the future, being an essential and non-reducible subject of prevention, as also the Covid-19 pandemic is demonstrating.

2.2. *Community cardiovascular prevention in an epochal change*

Individuals live in communities influencing their behavioural choices and here much remains to be done despite the evidence[47] and the recent recommendations, both American[48] and European[49,50]. The issue is significant because even if genetic risk was evaluated in the Khera study[33], among participants at high genetic risk, a favourable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavourable lifestyle. However, although there is evidence that lifestyle positive modifications can persist over time[51], the majority of these intervention studies do not confirm this pattern if begun after childhood[24,25] hence there is a clear need for antenatal, perinatal and primordial prevention[52]. Another possibility to find new ways of intervention is to investigate in depth into positive "natural experiments"[53] like the one occurred in Poland during the political transition[54]. Community cardiovascular prevention needs to be deeply innovated, integrating epidemiology, psychology, sociology, marketing science, statistics, informatics to find new ways to help communities to adopt a healthy lifestyles at every age, including pregnancy.

Notes

1. Rose G., *Rose's Strategy of Preventive Medicine*, with commentary by Kay-Tee Khaw and Michael Marmot, Oxford University Press, Oxford 2008, p. 38.

2. Dagan N., Barda N., Kepten E. (*et al.*), *BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting*, N Engl J Med, 2021;1412-1423.

3. Salomoni M.G., Di Valerio Z., Gabrielli E. (*et al.*), *Hesitant or Not Hesitant? A Systematic Review on Global Covid-19 Vaccine Acceptance in Different Populations*, Vaccines (Basel) 2021 Aug; 9(8): 873. Published online 2021 Aug 6. DOI: 10.3390/vaccines9080873.

4. The Lancet, *Latest global disease estimates reveal perfect storm of rising chronic diseases and public health failures fuelling Covid-19 pandemic* [available at http://www.healthdata.org/news-release/lancet-latest-global-disease-estimates-reveal-perfect-storm-rising-chronic-diseases-and; latest access 24/10/21].

5. GBD 2019 Diseases and Injuries Collaborators, *Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019*, Lancet 2020; 396: 1204-22 [see also http://www.healthdata.org/results/gbd_summaries/2019/cardiovascular-diseases-level-2-cause; latest access 20/11/21].

6. GBD 2019 Risk Factors Collaborators, *Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019*, Lancet 2020; 396: 1223-49 [see also http://www.healthdata.org/results/gbd_summaries/2019; latest access 20/11/21].

7. Last J.M. (ed. by), *A Dictionary of Epidemiology*, 4th edition, Oxford University Press, New York 2001.

8. Kannel W.B., Dawber T.R., Kagan A., Revotskie N., Stokes J. 3rd, *Factors of risk in the development of coronary heart disease—six-year follow-up experience*, The Framingham Study, Ann Int Med 1961;55:33-50.

9. Braunwald E., *The rise of cardiovascular medicine*, Eur Heart J, 2012;33:838-845.

10. Keys A., Aravanis C., Blackburn H. (*et al.*), *Seven Countries. A Multivariate Analysis of Death and Coronary Heart Disease*, A Commonwealth Fund Book, England, Harvard University Press, Cambridge, Massachussets and London 1980.

11. Intersalt Cooperative Research Group, *Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion*, BMJ 1988;297:319-328.

12. Kannel W.B., *An overview of the risk factors for cardiovascular disease*, in Kaplan N.M., Stamler J., *Prevention of Coronary Heart Disease*, WB Saunders Company, Philadelphia 1983.

13. Rose G., *Sick individuals and sick populations*, International Journal of Epidemiology, 1985;14:32-38.

14. Strasser T., *Reflections on cardiovascular diseases*, Interdiscip Science Rev, 1978;3:225–230.

15. Stamler J., Neaton J.D., Garside D.B., Daviglus M.L., *Current status: six established major risk factors – and low risk*, in Marmot M., Elliott P. (ed. by), *Coronary Heart Disease Epidemiology: From Aetiology to Public Health*, Oxford University Press, Oxford 2005, p. 46-54.

16. Pearce N., *Epidemiology in a changing world: variation, causation and ubiquitous risk factors*, Int J Epidemiol, 2011;40:503–512.

17. SCORE2 working group and ESC Cardiovascular risk collaboration, *SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe*, Eur Heart J 2021, 42:2439-2454.

18. Id., *SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions*. Eur Heart J 2021; 42: 2455-2467.

19. Goff D.C. Jr, Lloyd-Jones D.M., Bennett G. (*et al.*), *2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*, JACC, 2014, 63: 2935–2959.

20. Ferrario M., Chiodini P., Chambless L.E., Cesana G., Vanuzzo D., Panico S., Sega R., Pilotto L., Palmieri L., Giampaoli S., *Prediction of coronary events in a low incidence population: assessing accuracy of the CUORE Cohort Study prediction equation*, Int J Epidemiol, 2005;34:413-421.

21. Giampaoli S., Palmieri L., Donfrancesco C., Panico S., Vanuzzo D., Pilotto L., Ferrario M., Cesana G., Mattiello A., *On behalf of The CUORE Project Research Group. Cardiovascular risk assessment in Italy: the CUORE Project risk score and risk chart*, Ital J P Health, 2007; 4:102-109.

22. Palmieri L., Donfrancesco C., Giampaoli S., Trojani M., Panico S., Vanuzzo D., Pilotto L., Cesana G., Ferrario M., Chiodini P., Sega R., Stamler J., *Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: results from the Progetto CUORE*, Eur J Cardiovasc Prev Rehabil, 2006;13:562-570.

23. Giampaoli S., Palmieri L., Panico S., Vanuzzo D., Ferrario M., Chiodini P., Pilotto L., Donfrancesco C., Cesana G., Sega R., Stamler J., *Favorable cardiovascular risk profile (low risk) and 10-year stroke incidence in women and men: findings from 12 Italian population samples*, Am J Epidemiol, 2006;163:893-902.

24. Sidebottom A.C., Miedema M.D., Benson G. (*et al.*), *The impact of a population-based prevention program on cardiovascular events: Findings from the heart of new Ulm project*, Am H J, 2021, 239:38-51.

25. Fernández-Alvira J.M., Fernández-Jiménez R., De Miguel M. (*et al.*), *The challenge of sustainability: Long-term results from the Fifty-Fifty peer group-based intervention in cardiovascular risk factors*, Am H J, 2021, 240:81-88.

26. Kuulasmaa K., Tunstall-Pedoe H., Dobson A., Fortmann S., Sans S., Tolonen H., Evans A., Ferrario M., Tuomilehto J., *Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations*, Lancet, 2000;355:675-687.

27. Tunstall-Pedoe H., Vanuzzo D., Hobbs M., Mahonen M., Cepaitis Z., Kuulasmaa K. (*et al.*), *Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations*, Lancet, 2000;355(9205):688-700.

28. Tunstall-Pedoe H., Kuulasmaa K., Mahonen M., Tolonen H., Ruokokoski E., Amouyel P., *Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease*, Lancet, 1999;353(9164):1547-1557.

29. Karlinsky A., Kobak D., *Tracking excess mortality across countries during the Covid-19 pandemic with the World Mortality Dataset*, eLife, 2021;10:e69336 DOI: 10.7554/eLife.69336.

30. Hessamia A., Shamshiriande A., Heydaria K. (*et al.*), *Cardiovascular diseases burden in Covid-19: Systematic review and meta-analysis*, Am J Emergency Medicine, 2021, 382-391.

31. Marenberg M.E., Risch N., Berkman L.F., Floderus B., de Faire U., *Genetic susceptibility to death from coronary heart disease in a study of twins*, N Engl J Med, 1994, 330:1041-1046.

32. Lloyd-Jones D.M., Nam B.H., D'Agostino R.B. Sr (*et al.*), *Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring*, JAMA, 2004, 291:2204-2211.

33. Khera A.M., Emdin C.A., D. Phil., Drake I. (*et al.*), *Genetic risk, adherence to a healthy lifestyle, and coronary disease*, N Engl J Med, 2016;375:2349-2358.

34. Khera A.V., Chaffin M., Aragam K.G. (*et al.*), *Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations*, Nature genetics, 2018, 50:1219-1224.

35. Bolli A., Di Domenico P., Pastorino R., Busby G.B., Bottà G., *Risk of coronary artery disease conferred by low-density lipoprotein cholesterol depends on polygenic background*, Circulation, 2021, 143: 1452-1454.

36. Aragam K.G., Dobbyn A., Judy R. (*et al.*), *Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease*, JACC, 2020, 75:2769-2780.

37. Damask A., Steg P.G., Schwartz G.G. (*et al.*), *Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. 2020*, Circulation, 141:624-636.

38. Natarajan P., Young R., Stitziel N.O. (*et al.*), *Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting*, Circulation, 2017; 135: 2091-2101.

39. Frary C.E., Blicher M.K., Olesen T.B. (*et al.*), *Circulating biomarkers for long-term cardiovascular risk stratification in apparently healthy individuals from the MONICA 10 cohort*, Eur J Prev Cardiol, 2020;27:570-578.

40. Kozakova M., Palombo C., *Imaging subclinical atherosclerosis in cardiovascular risk stratification*, Eur J Prev Cardiol, 2021;28:247-249.

41. Faggiano P., Dasseni N., Gaibazzi N. (*et al.*), *Cardiac calcification as a marker of subclinical atherosclerosis and predictor of cardiovascular events: A review of the evidence*, Eur J Prev Cardiol, 2019;26:1191-1204.

42. Antonopoulos A.S., Angelopoulos A., Tsioufis K., Antoniades C., Tousoulis D., *Cardiovascular risk stratification by coronary computed tomography angiography imaging: current state-of-the-art*, Eur J Prev Cardiol, 2021;, zwab067, https://doi.org/10.1093/eurjpc/zwab067

43. Tamarappoo B.K., Lin Ab., Commandeur F. (*et al.*), *Machine learning integration of circulating and imaging biomarkers for explainable patient-specific prediction of cardiac events: a prospective study*, Atherosclerosis, 2021, 318: 76-82.

44. Quer G., Arnaout R., Henne M., Arnaout R., *Machine learning and the future of cardiovascular care*, JACC State-of-the-Art Review, JACC 2021, 77: 300-313.

45. Palmnäs M., Brunius C,. Shi L. (*et al.*), *Perspective: metabotyping – a potential personalized nutrition strategy for precision prevention of cardiometabolic disease*, Advances in Nutrition 2020, 11:524-532.

46. Traversi D., Pulliero A., Izzotti A. (*et al.*), *Precision medicine and public health: new challenges for effective and sustainable health*, J. Pers. Med, 2021, 11:135, https://doi.org/10.3390/jpm11020135.

47. O'Connor E.A., Evans C.V., Rushkin M.C. (*et al.*), *Behavioral counseling to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors Updated Evidence Report and Systematic Review for the US Preventive Services Task Force*, JAMA. 2020;324:2076-2094.

48. US Preventive Services Task Force, *Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors US Preventive Services Task Force Recommendation Statement*, JAMA, 2020;324(20):2069-2075.

49. Jorgensen T., Capewell S., Prescott E., Allender S., Sans S., Zdrojewski T., De Bacquer D., de Sutter J., Franco O.H., Logstrup S., Volpe M., Malyutina S., Marques-Vidal P., Reiner Z., Tell G.S., Verschuren W.M., Vanuzzo D., *PEP section of EACPR. Population-level changes to promote cardiovascular health*. Eur J Prev Cardiol, 2013;20:409-421.

50. Visseren F.L.J., Mach F., Smulders Y.M. (*et al.*), *2021 ESC Guidelines on cardiovascular disease prevention in clinical practice*, Eur Heart J, 2021; 42:3227-3337.

51. Journath G., Niklas Hammar N., Vikström M. (*et al.*), *A Swedish primary healthcare prevention programme focusing on promotion of physical activity and a healthy lifestyle reduced cardiovascular events and mortality: 22-year follow-up of 5761 study participants and a reference group*, Br J Sports Med, 2020;54:1294-1299.

52. D'Ascenzi F., Sciaccaluga C., Cameli M. (*et al.*), *When should cardiovascular prevention begin? The importance of antenatal, perinatal and primordial prevention*, Eur J Prev Cardiol, 2021; 28:361-369.

53. Sekikawa A., Horiuchi B.Y., Edmundowicz D. (*et al.*), *A "natural experiment" in cardiovascular epidemiology in the early 21st century*, Heart 2003;89:255-257.

54. Zatonski W.A., McMichael A.J., Powles J.W., *Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991*, BMJ, 1998; 316:1047-1051.

Globalisation and antibiotic-resistance epidemiology

Chronicles from the present and impact on a possible future

by Giancarlo Ceccarelli, Ornella Spagnolello, Gabriella d'Ettorre*

Abstract
Globalization has various effects on population health trends and significant implications on public health control. Among the most significant concerns, the rising antimicrobial resistance (AMR) rates and the spread of multi resistant microorganisms are of relevance. An analysis of the factors contributing to the problem is provided to offer an overview and stimulate debate on this key topic.

Running title: Travel and antibiotic resistances

Keywords: migrants, travel, globalization, antibiotic resistances, multidrug resistance, MRD organism, MDRo.

Back in 1962, Hebert Marshall McLuhan first introduced the concept of "global village" into his manuscript "Gutenberg Galaxy": "the world is becoming a global village, a community in which distance and isolation are overcome"[1].

Since then, along with the spreading of globalization we assisted to a reduction on transit time across the world with a quicker mobilization of people and items. This phenomenon, together with the demographic growth and the urbanization on the rise, led to a global spread of pathogens from different areas along with their own carriers. Despite many studies addressed the topic of the spreading antibiotic-resistance on a global scale, at the moment, given their methodological diversity, no conclusive data emerged on the size of the problem and potential factors involved in the spread. However, consistent differences in antibiotic-resistance epidemiology were recorded in different geographical areas according with the "Antimicrobial resistance: global report on surveillance" issued by World Health Organization (WHO)[2].

Multiple factors are involved in the rapid emergence of antibiotic-resistance: over-

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use and misuse of these medications in both infections and prophylaxis, the extensive use in agriculture and the wide deployment as growth supplements in livestock.

Generally speaking, the lack of regulation and monitoring in many countries, together with the impact of globalization, have led not only to the selection but also to the spread of drug-resistant species.

On the grounds of these wide geographical differences in antibiotic-resistance prevalence, other epidemiological factors (such as migration flows, tourism, trade in goods and climate changes) act to amplify the possibility of spread.

1. Migration flows and antibiotic-resistance

There is an increasing body of evidence that human movements facilitate the global spread of resistant bacteria and antimicrobial resistance genes. In particular, the rising antimicrobial resistance (AMR) rates in developing countries, both in healthcare settings and in the community, represent a risk factor for the spread of MDR pathogens especially if these countries are starting points of large migratory flows[3]. Factors facilitating the acquisition and transmission of MDR pathogens among mobile migrants are collapsed housing, hygiene, and healthcare infrastructures in communities of origin as well as poor hygiene conditions during the trip to destination countries[4]. Epidemiological data concerning the relationship among migrant flows and spread of antibiotic-resistance are not conclusive given the methodological diversity of studies carried out till now. However, a recent meta-analysis based on 23 observational studies for a total of 2.319 migrants included from 2000 to 2017 in Europe, showed that the prevalence of any antibiotic-resistance carriage or infection in the given population was 25.4% (CI 95%, 19,1-31,8). This pooled prevalence was higher in refugees and asylum seekers than in other migrants' groups (33.1%, 11.1-55.1). Regarding methicillin-resistant *Staphylococcus aureus* (MRSA) the prevalence was 7.8% (4.8-10.7) whereas antibiotic-resistant Gram-negative bacteria prevalence was 27.2% (17.6-36.8). Interestingly, no evidence of high rates of transmission of antibiotic-resistance from migrant to host populations was found[5].

2. Role of tourism

International travelers returning from high prevalence AMR destinations to their own countries are possible carriers for resistant microbes acquired through the journey. Moreover, multiple studies showed that the chance of acquiring multi-drug resistant Enterobacteriaceae are related to the local prevalence in the destination area and ranges from 21 to 51% in healthy travels coming from low prevalence area. Trips to Asia or Indian Subcontinent are at major risk for the acquisition of ESBL (extended spectrum beta-lactamase) Enterobacteriaceae or CRE (carbapenem resistant Enterobacteriaceae) with rate of travel-related fecal colonization up to 85%. Lower but still consistent rate of colonization were found for travels to Africa or Middle East countries (13-44%).

Among risk factors for colonization, gastrointestinal discomfort, diarrhea, health care assistance in the destination county and misuse of antibiotics emerged as particularly relevant. High-endemic areas as travel destination was also identified as a major risk factor for the acquisition of Enterobacteriaceae multi-drug resist-

ant, including urinary tract infections[6,7].

Particularly interesting is the case of travelers who undergo hospital admission during their journey. One report carried out in Finland and including 1.122 travelers coming back from their destination after having had an occasional hospitalization abroad revealed a rate of multi-drug resistant bacteria colonization of 55% for those coming from tropical areas and 17% from temperate zone. Colonization rates proved highest in those returning from South Asia (77.6%), followed by those having visited Latin America (60%), Africa (60%) and East and Southeast Asia (52.5%). Independent risk factors for colonization were travel destination, time from hospital discharge, young age, surgical surgery and antibiotic administration[8].

3. Medical tourism

Foreigners seeking medical care are another relevant source for the spread of multi-drug resistant bacteria. In 2018, up to 11 million of persons moved abroad for medical purposes. In this particular population, the risk of becoming drug resistant carriers was estimated to be higher in comparison to the local population. In line with this, a recent study carried out in Israel showed that foreign patients seeking advanced medical care had a 6 to 10-fold higher risk to carry multi-drug resistant bacteria than the resident population. Moreover, this risk resulted associated to the microbiological epidemiology of both the local and the origin country[9].

4. Global trade and antibiotic resistance

The development of resistant pathogens has been attributed not only to increased antibiotic use in hospitals and outpatient facilities but also to veterinary applications and as a result of physical processes used in food production and preservation processes[10].

An interesting example, in this sense, is the recent observation of a major increase of colistin resistance (MCR-1) during a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China[11].

This new resistance was then identified in humans, food-producing animals, pets and food[12]. Nowadays, MCR-1 has been spreading in over 30 countries as a result of colistin use in food-processing industry[13].

Although potentially relevant, the role of global trade in the spread of resistant bacteria and antimicrobial resistance genes has been poorly explored so far. Unlike human use which appears to be better subject to shared regulations, the use of antimicrobials in the area of food production and in the veterinary field, for example for auxological purposes, is often not subject to univocal international rules. The national and international regulation of food/trade linkage is critical in the control of the potential spread of AMR. However currently, regulations on AMR are problematic mostly in settings where political commitment or bureaucratic capacity to regulate is weak[14].

5. Relative impact of the different determinants on spread of drug-resistant species

In recent years, developed countries and in particular Western Europe have experienced significant influx of

migrants and refugees owing to ongoing conflicts, political and economic instability, and humanitarian crises in some African and Asian regions. Despite available data suggest that migrants can be the carriers of a significant burden of multidrug-resistant (MDR) organisms, other factors contribute more substantially to the global spread of AMR. In fact, the International Organization for Migration reported that 257.7 million migrants worldwide in 2017; but in the same period the World Tourism Organization reported 1.4 billion tourists worldwide (of which 11 million for medical treatment, as indicated by the Medical Tourism Association) and 7.1 billion passengers used an air flight (ACI Annual World Airport Traffic Report). Finally, the World Bank reported that 750 million cargo shipping containers were shipped in 2016. On the basis of these data, it is evident that the potential contribution of the various determinants to the spread of AMR is profoundly different, relegating the risk associated with migratory flows to an apparently supporting role.

6. Conclusions

Globalization is an irreversible process with serious and poorly controllable implications on health care. In order to prevent and control the spread of antibiotic resistance worldwide, WHO has supported a robust international action plan to tackle the problem, mainly based on:

- Improving surveillance of antibiotic-resistant infections;
- Strengthen policies, programs, and implementation of infection prevention and control measures;
- Regulate and promote the appropriate use and disposal of quality medicines;
- Make information available on the impact of antibiotic resistance.

However, considering the lack of awareness of many nations, in 2019 WHO listed the spread of antibiotic resistances among the top 10 global public health threats facing humanity and advocated the research in new class of antibiotics and diagnostic tools considering the difficulty of all countries involved.

Notes

1. McLuhan H.M., *The Gutenberg Galaxy: the making of typographic man*, Routledge & Kegan Paul, 1962 (ISBN 0-7100-1818-5).

2. World Health Organization, *Antimicrobial resistance: global report on surveillance*, 2014 [available at https://apps.who.int/iris/bitstream/handle/10665/112642/9789241564748 _eng.pdf; jsessionid=-D0A9CC6536C3D3AB03CDEA7251805C67?sequence=1 (accesso in data 25/3/2019].

3. Maltezou H.C., Theodoridou M., Daikos G.L., *Antimicrobial resistance and the current refugee crisis*, Journal of Global Antimicrobial Resistance, September 2017 [10:75-79. doi: 10.1016/j.jgar.2017.03.013. Epub 2017 Jul 1. PMID: 28673700].

4. Nellums L.B., Thompson H., Holmes A. (*et al.*), *Antimicrobial resistance among migrants in Europe: a systematic review and metaanalysis*, Lancet Infectious Diseases, 2018, 18(7):796-811.

5. Langford B.J., Schwartz K.L., *Bringing home unwelcome souvenirs: Travel and drug-resistant bacteria*, Canada Communicable Disease Report, 2018, 44(11):277-82.

6. Ruppé E., Andremont A., Armand-Lefèvre L., *Digestive tract colonization by multidrug-resistant Enterobacteriaceae in travellers: An update*, Travel Medicine and Infectious Disease, 2018, 21:28-35.

7. Khawaja T., Kirveskari J., Johansson S. (*et al.*), *Patients hospitalized abroad as importers of multiresistant bacteria-a cross-sectional study*, Clinical Microbiology and Infection, 2017, 23(9):673.e1-673.e8.

8. Benenson S., Nir-Paz R., Golomb M. (*et al.*), *Carriage of multi-drug resistant bacteria among foreigners seeking medical care*, Scientific Reports, 2018; 8(1):9471.

9. George A., *Antimicrobial Resistance (AMR) in the Food Chain: Trade, One Health and Codex*, Tropical Medicine and Infectious Disease, 2019, 4(1):54.

10. Liu Y.Y., Wang Y., Walsh T.R. (*et al.*), *Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study*, Lancet Infectious Diseases, 2016, 16(2):161-8.

11. European Centre for Disease Prevention and Control, *View: Maps for Plasmid-mediated Colistin Resistance in Enterobacteriaceae* [available at https://ecdc.europa.eu/en/publications-data/view-maps-plasmid-mediated-colistin-resistance-enterobacteriaceae; latest access 25/3/2019].

12. George A., *Antimicrobial resistance, trade, food safety and security*, One Health, 2017, 5:6-8.

The pandemic is increasing gender inequalities and minority disparities

Universities must take the lead

by Angelica Varesi, Lorenzo Rossi, Valentina Floris, Giovanni Ricevuti*

Abstract
International student mobility has always represented an advantage in terms of globalization, sharing of ideas, collaboration, innovation and cultural exchange. However, the Covid-19 pandemic outbreak severely limited international travels, thus making it impossible to carry out Erasmus traineeships and summer internships abroad. Although mobility and exchanges are slowly recovering, the impact that the lack of internalization has determined on undergraduates is still uncertain. Moreover, increased disparities between men and women as well as between researchers from richer and poorer countries are also a rising concern among global health experts. Here we briefly present a case study as a starting point for a more general discussion on the consequences that the Covid-19 pandemic can have for students' future, women's career and under-represented groups' success, with particular focus on the biological field.

1. Introduction

In December 2019, TZ, a biology student enrolled at the University of Pavia, Italy, was accepted for a summer internship at the Icahn School of Medicine at Mount Sinai, New York, USA. "After a brief interview, my dream came true, I was so excited! I was finally able to seize a great opportunity for my future, and forge important partnerships for postgraduate", said TZ. However, in March 2020 the situation in Italy suddenly changed, and the lockdown was imposed by the authorities. At first, no one thought that the mobility block would have lasted long but, shortly after, the pandemic took over, and international travel, as well as intranational travel, was banned. Even worse, travel between the United States and Europe was deemed to be at high risk, and every and all flights were canceled, with few exceptions. Unsurprisingly, in May 2020 came the decision from the Mount Sinai to reject

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any foreign students previously accepted for internships, due to safety concerns. "When I read the rejection email, the world fell on me for a moment. The commitment and the tenacity with which I had obtained that internship had been thwarted in one shot. I had no idea on how to replace this internship, and I started writing random emails all over Italy and Europe, hoping to find a PI who had a free place in his/her lab". However, all answers were negative, and the effort of TZ was useless. The need to keep social distancing and the work shifts obligation made accepting new students impossible even for PhD candidates, let alone undergraduates. "I cannot predict the damage that losing an internship in the US has done on my future career, but the pandemic certainly left its mark". In the biological field, having substantial practical experience before graduation is an essential prerequisite for applying to a PhD position, and students like TZ lost an important opportunity to improve their research expertise. Moreover, travelling and living in the United States is expensive, and the scholarships won for 2020 will hardly be reassigned for future years, leaving a gap in the career of early scientists. "After a period of discouragement due to all those rejections, I began to concentrate on improving my soft skills. There were a lot of public speaking free online courses on the web, so I decided to fill my summer like this. After all, the important thing is looking for new stimuli". Thanks to these webinars, TZ can now ask questions at conferences without fear, but the question remains whether the soft and hard skills acquired in the US could have been many more.

2. Results

2.1. *The effect of the pandemic psychological distress*

TZ is not the only student who lived this experience. Stories like the one reported here have impaired many bright and willing students to achieve their dream[1,2]. When, in July 2020, the president of the United States Donald Trump imposed Visa restrictions for foreign students whose institutions offered online teaching only, enrolment in US graduate programs was forbidden to many international applicants, similarly to what happened to TZ[3]. Given this situation, it is understandable that feelings of uncertainty and desolation pervaded students around the world who aspired to build a brilliant career in North America[4].

The Covid-19 pandemic has also exacerbated cognitive symptoms among college youth. Although in the biological field anxiety, stress and depression have been reported due to the constant pressure of the "publish or perish" culture, they have grown at even higher extent during the pandemic[5]. The results of a survey involving 30,000 undergraduates and more than 15,000 graduate students, conducted by a collaboration between the University of Minnesota and the University of California, report that anxiety increased by 50% in 2020 compared to 2019 (Woolston, 2020b). Signs of depression followed the same rising trend, as noted by another survey involving 19,000 students in the US[6]. When Universities were forced to close, and lab work was restricted to few exceptions, isolation and loneliness were also reported by other students[5]. In addition, those who already presented mental health disorders often experience an increase in drug abuse and alcohol consumption[7]. In

this respect, a study conducted in Ohio demonstrated that the average number of drinks per week among students passed from 3,5 before the pandemic to more than 5 after the lockdown[8]. Given these data, the idea of a psychological support offered by the Universities, already applied in the USA, could prove beneficial in reducing stress and anxiety among young students and researchers, thus helping to get them out from the mental impact of the pandemic.

2.2. *Minorities and under-represented groups pay the price*

Several students belonging to minorities have come to meet the same challenges of TZ, but the fear that the under-represented groups will pay the highest price is great. "Skipping a summer internship for a Black student or a White student is not the same" warns Giovanni Ricevuti, coordinator of the Erasmus program at the University of Pavia, Italy. "We often forget that students living in richer countries have countless other possibilities to enrich their CVs that students from under-represented groups just don't have. For African students, for example, losing the chance of going to the US or Europe to carry out high-impact research is often detrimental for their career, and no one will give them back this opportunity".

An increasing number of accounts is dramatically reporting that several Universities all over the world are not ready yet to ensure fairness and inclusion in the application process, as many are shifting their focus from promoting diversity towards developing measures that allow students and workers to attend safely again their Universities (Nwora *et al.*, 2021; Woolston, 2020a). But safe does not mean equal: "It's like we are going back 30 years", said Raìsa Vieira, a Brazilian ecologist at the Federal University of Goiás in Goiânia, when interviewed from Nature Journal[9]. As online teaching and smart working are deemed necessary to allow the continuation of daily activities, it has to be acknowledged that not everyone has access to the same opportunities. Indeed, despite the great adaptation effort of some Universities to run all courses from remote[11], students belonging to minorities in some cases had no Internet access, thus being unable to work from home, as the case of the Indian PhD student Ganguly[5]. Hope remains, that lagging Universities and funding Institutions will follow the path traced by the prompt response of others in order to promote inclusion in the application procedure: "proposing a balanced selection has always been our priority and will continue to be so even when the pandemic is over", reassured Giovanni Ricevuti.

The impact of the pandemic on under-represented groups goes even beyond the lack of strategic support and equal opportunities during application processes. Indeed, ethnic minorities are reported to be more likely affected by the economic consequences of the pandemic, and financial disparities are predicted to rise among Black scientists, thus increasing inequalities[9]. "Many had to decide between their family in one country and their students and projects in another country", warns Bea Maas, ecologist at the University of Vienna, who witnessed several fellow researchers leaving their workplace to fly back to their hometowns to take care of their families[9]. While pre-pandemic data already showed that poverty rates in the US are two-to-three times higher for ethnic minorities

compared to Whites[12], the impact of the novel coronavirus seems to have exacerbated the inequality or at least the perception of it. Indeed, a survey conducted by sociologists from the Indiana University (US) reported that – during the Covid-19 pandemic – Whites experienced significantly less financial, housing and food insecurity than ethnic minorities such as Black, Latino and others[13]. Furthermore, in the same study, a similar trend has been observed between individuals bearing a different degree of education, with less educated ones most hardly hit by the consequences of the pandemic (Perry *et al.*, 2021).

Worsening the scenario, the current economic crisis turned out to be associated also with a higher prevalence of infection. African Americans, lowest income groups and women have been shown to be at higher risk of contracting Covid-19 infection compared to the rest of the population, according to data collected in Michigan, US[14].

The fact that the novel coronavirus represented anything but an event flattening pre-existing discrepancies among different social subgroups is well documented by the not alike risks of pandemic-related death and hospitalization among ethnic groups[15]. Once more, data collected in the US show that minorities, in particular Black and Latino persons, have faced significant higher rate of hospitalization or Covid-related death compared to Whites, and often in higher proportions than one would estimate based on the number of infected persons per ethnic group[15]. Multiple causes seem to be at the root of these recurring inequalities: differential access to the health systems and to higher education, pre-existing comorbidities and discrepancies in financial and work-related situations, among them[15,16]. Hence, it appears as a priority to invest time and energies at different societal levels, Universities first, in order to plan global health and economic strategies to flatten unfair differences among individuals and to reverse the negative trend that the Covid-19 pandemic has fostered about pre-existing issues such as diversity and inclusion[9].

2.3. *Increased gender inequality in the pandemic era*

Enhanced gender inequality as a result of Covid-19 lockdown is also of concern. Disproportions in employment because of the pandemic have been reported across different countries[17]. Results from a longitudinal study conducted in the UK reports that White men had a lower probability to be dismissed from work between March and May 2020, while women and ethnic minorities were more likely to experience economic hardship[18]. Similar data were also obtained in the US, where the penalty of being mothers emerged as a consequence of unequal layoffs in the Covid-19 pandemic[19]. In India, where women have always been subject to the gender hierarchy, Covid-19 pandemic has drastically worsened their conditions. Socioeconomic precariousness, job loss and economic uncertainty all contributed to increasing the gap of inequality[20]. Although it is often difficult to quantify the impact of the pandemic on women, results from a six-country survey calculate that women have a 24% higher probability of being fired compared to their male counterparts. At the same time, a decrease in women's income of more than 50% compared to men's one is also expected, with a strong impact on expenditures and savings[21]. In this respect, interventions aimed at supporting women should be considered. For example,

economic benefits in favor of unemployed women should be introduced by governments, with a particular attention to mothers and pregnant women[22].

With reference to the scientific field, the fact that young women are reported to be one of the categories most affected by the pandemic[23] is of particular concern for their career. The results of a survey involving 3,345 Brazilian academics show that while 77% of White men without children managed to publish by the planned deadline during the pandemic, only 47% of women with children were able to do the same[24]. When mothers or single parents need to look after their children during homeschooling, do cleaning and cooking, it becomes difficult to concentrate on analyzing data and writing papers, with a strong impact on their mental health[25,26]. Moreover, reduced physical exercise among women compared to men because of the aforementioned household chores should also be accounted as a sign of inequality[27]. Given these conditions, symptoms like psychological distress are common. Unsurprisingly, Xue and McMunn report that lone mothers are at higher risk of experiencing excessive stress and decreased mental health, with serious consequences on labor activity[28]. "When your PI asks you to be productive and to quickly conclude your manuscript while you need to accomplish an infinite number of tasks at the same time, a rise in pressure is understandable", says professor Ricevuti. Often, working at nights remains the only solution to be able to do everything in 24 hours, but that's not always enough. According to a paper published in 2020 in the BJM Glob Health Journal, women account for only a third of the authors who published manuscripts in the Covid-19 field, with a high prevalence of men in the first and last positions[29]. Andreson and colleagues point out how this reduction could be particularly relevant for early-career women, thus making them start at a disadvantaged level compared to their male counterparts[30]. In biology, not publishing means not accessing grants, and the difference in productivity between males and females will be detrimental to access research funds. In Denmark, one of the European countries with the highest gender gaps, the situation could get very serious, and the effects of the pandemic on productivity might slow down any attempt to flatten the differences[31]. Extended deadlines, enhanced inclusion, policy revision and funding distribution considering the gender consequences of the pandemic should be considered in granting assignments, PhD/postdoc's candidate evaluation and mobility fellowship selection. "Different circumstances cannot be simply compared but must be analyzed and understood singularly. I hope the evaluation committee will take this into account", advises professor Ricevuti.

3. Discussion

Experiences like that of TZ are only an example of how the pandemic is affecting the entire research world, from undergraduates to postdocs and group leaders. In addition to those who could not leave for a summer internship, there are those who were unable to publish or that lost important funding, therefore exacerbating the already reported signs of stress, anxiety and depression among people involved in the academia field. Financial distress, unemployment and economic hardship have been reported to be higher among ethnic minorities and women, thus suggesting that already disadvantaged

groups are the mostly affected by the pandemic consequences[13]. Since under-represented groups and women are paying the highest price of both the lockdown and the economic crisis, their disparities must be considered by the research community. The aim of our paper is to shed light on the challenges that minority groups and women are facing because of the pandemic. To avoid the increase in inequality, Universities, Institutions and Committees must revise their relevant policy quickly, implementing a flexible and balanced grading system when awarding research grants, mobility fellowships/internships and job promotion. We strongly call for a revision of the currently used evaluation parameters, and we hope that this action can have positive results in limiting disparities and in reducing the gender gap.

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AV, LR and VF wrote and revised the manuscript. GR supervised the work and revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

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Notes

1. Gould J. The career costs of Covid-19: how postdocs and PhD students are paying the price. Nature (2020) available at https://www.nature.com/articles/d41586-020-03108-4 Accessed on 28/11/2021

2. Reardon S. More international students were coming to US universities - then Covid hit. Nature. 2020 Nov 9. doi: 10.1038/d41586-020-03168-6.

3. Kumar S. How to manage the uncertainty of a remote PhD. Nature. 2021 Jul 20. doi: 10.1038/d41586-021-02001-y.

4. Arnold C, Woolston C. Uncertainty plagues junior researchers from underprivileged backgrounds amid pandemic. Nature. 2020 Dec;588(7837):355-357. doi: 10.1038/d41586-020-03465-0.

5. Forrester N. Mental health of graduate students sorely overlooked. Nature. 2021 Jul;595(7865):135-137. doi: 10.1038/d41586-021-01751-z.

6. Woolston C. Signs of depression and anxiety soar among US graduate students during pandemic. Nature (2020) 585:147-148; doi: 10.1038/d41586-020-02439-6.

7. Lechner W v., Laurene KR, Patel S, Anderson M, Grega C, Kenne DR. Changes in alcohol use as a function of psychological distress and social support following Covid-19 related University closings. Addictive Behaviors (2020) 110:106527 doi:10.1016/j.addbeh.2020.106527

8. Woolston C. 'The problem is greater than it's ever been': US universities urged to invest in mental-health resources. Nature (2021) 590:171-172. doi: 10.1038/d41586-021-00229-2

9. Woolston C. 'It's like we're going back 30 years': how the coronavirus is gutting diversity in science. Nature (2020), doi: 10.1038/d41586-020-02288-3

10. Nwora C, Allred DB, Verduzco-Gutierrez M. Mitigating Bias in Virtual Interviews for Applicants Who are Underrepresented in Medicine. Journal of the National Medical Association (2021) 113:74-76, doi:10.1016/j.jnma.2020.07.011

11. Padma T. How Covid changed schools outreach. Nature (2021) 594:289-291. doi: 10.1038/d41586-021-01517-7

12. Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The Disproportionate Impact of Covid-19 on Racial and Ethnic Minorities in the United States. Clinical Infectious Diseases (2021) 72:703-706, doi:10.1093/cid/ciaa815

13. Perry BL, Aronson B, Pescosolido BA. Pandemic precarity: Covid-19 is exposing and exacerbating inequalities in the American heartland. Proceedings of the National Academy of Sciences (2021) 118:e2020685118, doi:10.1073/pnas.2020685118

14. Wu K-HH, Hornsby WE, Klunder B, Krause A, Driscoll A, Kulka J, Bickett-Hickok R, Fellows A, Graham S, Kaleba EO, et al. Exposure and risk factors for Covid-19 and the impact of staying home on Michigan residents. PLOS ONE (2021) 16:e0246447, doi:10.1371/journal.pone.0246447

15. Center for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. (2021)

16. Razai MS, Kankam HKN, Majeed A, Esmail A, Williams DR. Mitigating ethnic disparities in covid-19 and beyond. BMJ (2021) 372:m4921, doi:10.1136/bmj.m4921

17. Landivar LC, Ruppanner L, Scarborough WJ, Collins C. Early Signs Indicate That Covid-19 Is Exacerbating Gender Inequality in the Labor Force. Socius: Sociological Research for a Dynamic World (2020) 6:2378023120947997, doi:10.1177/2378023120947997

18. Witteveen D. Sociodemographic inequality in exposure to Covid-19-induced economic hardship in the United Kingdom. Research in Social Stratification and Mobility (2020) 69:100551 doi:10.1016/j.rssm.2020.100551

19. Dias FA, Chance J, Buchanan A. The motherhood penalty and The fatherhood premium in employment during covid-19: evidence from The united states. Research in Social Stratification and Mobility (2020) 69:100542 doi:10.1016/j.rssm.2020.100542

20. Chakraborty D. The "living dead" within "deathworlds": Gender crisis and Covid-19 in India. Gender, Work & Organization (2021) 10.1111/gwao.12585, doi:10.1111/gwao.12585

21. Dang H-AH, Viet Nguyen C. Gender inequality during the Covid-19 pandemic: Income, expenditure, savings, and job loss. World Development (2021) 140:105296, doi:10.1016/j.worlddev.2020.105296

22. Steinert JI, Alacevich C, Steele B, Hennegan J, Yakubovich AR. Response strategies for promoting gender equality in public health emergencies: a rapid scoping review. BMJ Open (2021) 11:e048292, doi:10.1136/bmjopen-2020-048292

23. Davillas A, Jones AM. The first wave of the Covid-19 pandemic and its impact on socioeconomic inequality in psychological distress in the UK. Health Economics (2021) 30:1668-1683, doi:10.1002/hec.4275

24. Staniscuaski F, Kmetzsch L, Soletti RC, Reichert F, Zandonà E, Ludwig ZMC, Lima EF, Neumann A, Schwartz IVD, Mello-Carpes PB, et al. Gender, Race and Parenthood Impact Academic Productivity During the Covid-19 Pandemic: From Survey to Action. Frontiers in Psychology (2021) 12:663252, doi:10.3389/fpsyg.2021.663252

25. Staniscuaski F, Reichert F, Werneck FP, de Oliveira L, Mello-Carpes PB, Soletti RC, Almeida CI, Zandona E, Ricachenevsky FK, Neumann A, et al. Impact of Covid-19 on academic mothers. Science (2020) 368:6492, doi:10.1126/science.abc2740

26. Reardon S. Pandemic measures disproportionately harm women's careers. Nature (2021), doi: 10.1038/d41586-021-00854-x

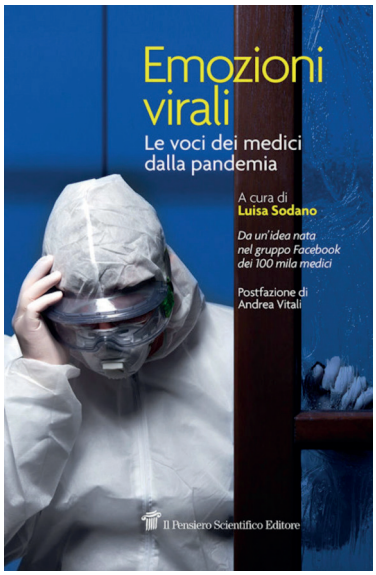
27. Sher C, Wu C. Who Stays Physically Active during Covid-19? Inequality and Exercise Patterns in the United States. Socius: Sociological Research for a Dynamic World (2021) 7:2378023120987710, doi:10.1177/2378023120987710

28. Xue B, McMunn A. Gender differences in unpaid care work and psychological distress in the UK Covid-19 lockdown. PLOS ONE (2021) 16:e0247959, doi:10.1371/journal.pone.0247959

29. Pinho-Gomes A-C, Peters S, Thompson K, Hockham C, Ripullone K, Woodward M, Carcel C. Where are the women? Gender inequalities in Covid-19 research authorship. BMJ Global Health (2020) 5:e002922, doi:10.1136/bmjgh-2020-002922

30. Andersen JP, Nielsen MW, Simone NL, Lewiss RE, Jagsi R. Covid-19 medical papers have fewer women first authors than expected. eLife (2020) 9:e58807, doi:10.7554/eLife.58807

31. Bendixen M, Hall VJ. How the pandemic could choke gender equity for female researchers in Denmark. Nature. 2020 Sep 9. doi: 10.1038/d41586-020-02527-7.



A comment on

Emozioni virali. Le voci dei medici dalla pandemia*

by Maria Gabriella Buzzi, Luisa Sodano**

The unprecedented and unexpected Covid-19 pandemic caused by the new coronavirus Sars-CoV-2 forced medical doctors to upset their daily working routine, to convert entire hospitals in Covid-19 units and to abandon their own private daily living. During pandemic Phase 1 Italian doctors had to face up an extraordinary experience suddenly after Sars-CoV-2/Covid-19 spread in China in early 2020. Abnegation and compassion were the mighty forces driving their unceasing work. The unmet needs of adequate coping and treating patients because of the novelty and the peculiarity of the infection/disease, along with the unpreparedness to the pandemic, found the place for discussion in a newborn social group, the so-called "The 100,00 doctors Facebook group", that spontaneously and rapidly had become the source of information, discussion and management proposals. Meanwhile, it was also the place in which inner and covert emotions found their wording that eventually gave rise to a collection of short stories that has become a book entitled *Emozioni virali. Le voci dei medici dalla pandemia*. This anthology, reporting personal and professional experiences, may serve as a history book to teach next generation, to keep memory of the unique time during the Sars-CoV-2/Covid-19 pandemic Phase 1, to help in improving the Italian Health System and to emphasize the positive role of digital communication, when properly used.

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Emozioni virali, Le voci dei medici dalla pandemia is dedicated to all victims of Covid-19 and royalties will be donated to families of doctors who did not survive the pandemic.

By the time the new coronavirus Sars-CoV-2 was expanding in China and starting its mad rush all over the world, and Codogno (Lodi, Italy) hosted the first recognized Italian Covid-19 case (February 21, 2020), a Facebook group of Italian physicians was reconverted to address specifically the new virus and the related disease ("Coronavirus, Sars-CoV-2 e Covid-19 gruppo per soli medici" https://www.facebook.com/groups/Coronavirusmediciitaliani/).

In a few weeks the site registered more than 100,000 physicians and was overloaded by posts from any type of medical specialists reporting the critical conditions in which they were working, describing any kind of Covid-19 symptoms, asking for suggestions, getting infected and undergoing treatments, sometimes in Intensive Care Unit from where, until possible, they described any single feature and disease progression. During the first few weeks, along with respiratory features of the disease, many other characteristics were enlightened and provided clues for recognizing Covid-19 even in the absence of respiratory symptoms in non-hospitalized people. Hypo/anosmia and hypo/ageusia were continuously reported and were learnt as the most common and heralding symptoms of the disease, showing the early involvement of the neurological system and leading to the hypothesis of a direct portal of entry of the virus from the nose to the brain that resulted in severe complication of Covid-19 (i.e., ischemic or haemorragic stroke) seen in hospitalized patients. Alert on those and other symptoms and signs such as cutaneous manifestations of Covid-19, was crucial for helping to rapidly identify patients who could be the source of infection for other persons. Anatomo-pathological findings were often described in the group and many of the information served to better understand the mechanisms of the disease as well as to hypothesize adequate treatment, since the Sars-CoV-2 virus and its related disease, Covid-19, were completely new.

Meanwhile, the group was the environment in which personal feelings emerged as if it was the only place where to talk about and share the emotional side of the pandemic experience. In this context, on April 23, 2020, Luisa Sodano, Epidemiologist, who had registered into the group shortly before, posted her idea of collecting somehow this emotional part of the story. Within two weeks many physicians sent their short stories, mostly from Northern Italy, 37 of which became the body of the book.

The preface written by Camillo Il Grande, Gastrointestinal Surgeon, the founder physician of the Facebook group, underlines the role of the group as the privileged hub to discuss, exchange opinions, ask and provide support. As Camillo says, the book is "the natural evolution of self-awareness and confrontation" that evolved during the pandemic "Phase 1" within the group where any doubt, any help request, any information, any feeling or fear could be collected and treasured.

The introduction, written by the editorial committee members (Patrizia Iolanda Ambruoso, Marina Bianchi, Maria Gabriella Buzzi, Giuliana Crisman, Marcello Marcelli, Stefania Mostaccioli, Luisa Sodano and Marco Solaro) outlines the content of the sections of the book expressing the condition in which any physician/writer was carrying out her/his job. The unmet needs and the spasmodic search to cope with the virus and its related disease were the core of the discussion. Meanwhile, the sense of solidarity that emerged within the group and that would result into the so called "collateral affections", led to the idea that such a piece of history, as it was experienced by physicians (and all other health workers), deserved to be acknowledged and possibly recollected in the future. Therefore the "leading actors" had to write it down, there and then, before losing the inner emotional component. The humaneness, including sense of impotence, powerlessness, and loneliness are the leading feelings throughout the book, common to both physicians and patients.

The five sections have specific tracks on the basis of the role that any physician/writer had in her/his medical activity. The first section of the book, "The context" is an overview of the conditions in which the Sars-CoV-2 pandemic spread in Italy. First of all, the lack of an updated Italian pandemic plan revealing the poor capacity of Italy to face up to the pandemic, and then the doubtful news from China and the uncertainty of WHO, the speedy rush of the virus in Northern Italy and the premise to the national lockdown, the difficulties in creating an adequate monitoring-tracing system to identify clusters and isolate cases, and eventually, the overwhelming daily number of victims and the need of relocating corpses outside Bergamo where there was not enough room for burying them, through the Italian Army trucks. This was, and still is, the hardest picture and the worst remembrance of Covid-19 pandemic "Phase I". In the following sections, "With bare hands", "Cities and countryside", "Dear Colleague, will you help me?" and "The rearguard", 37 stories describe the many different conditions that Doctors had to face during pandemic Phase I.

"The literary category to which the work is attributable can be identified as narrative medicine. [...] Narrative medicine are also stories that look at epidemics not from a medical-scientific point of view, but, in fact, from a literary perspective. [...] The narratives that come from the very experience of illness are of a different nature. In English, this production is collected under the label of "misery report", or stories of suffering induced by pathologies and treatment paths (misery in this context means adversity, misfortune, suffering)". This is the way Sandro Spinsanti, Bioethicist, qualifies the book *Emozioni virali* (https://sandrospinsanti.eu/la-pandemia-e-i-suoi-affetti-collaterali/). In his comment, Spinsanti highlights some of the prevailing emotions that emerge in reading the stories. Among those, the sense of pride in the profession and "no triumphalism under the much vaunted profile of heroes and angels: simply a regained awareness, on the ground of a commitment in extreme conditions", along with the awareness of being vulnerable.

As was said before, this "anthology" springs from the

need of describing personal experiences to testify in real time a crucial worldwide moment. *Emozioni virali* is therefore an interesting and unique history book that may serve in the future as a teaching book to communicate with next generations.

Besides, the awareness of unpreparedness and the urge to complain about an inadequate Health System, call for a thorough revision. The reported experience may serve to lay the foundation for a renewed public Health System. As a reader of *Emozioni virali* said, "This book contains a 30-year project for the next Italian Health System".

Finally, the way *Emozioni virali* came to life in the middle of lockdown, emphasizes the potential of digital communication. The "100,000 doctors Facebook group" is, in fact, the first and, so far, the largest, ongoing social network specifically devoted to the pandemic. *Emozioni virali* has been completely built through digital communication and virtual meetings of the editorial committee late at night after tough working days and amazingly it came to life as a handling and tangible object. Most of the physicians/writers have not had a chance to meet in person yet. The book has been presented mostly in virtual meetings or through mass media (newspapers, national radio and TV channels). However, among the few "in presence" presentations, it is noteworthy to recall the ones in Lombardia: in Martinengo (Bergamo) on July 16, 2020, and in Milan on September 30, 2020, a tribute to a region who experienced the worst impact of Sars-CoV-2 pandemic and the largest toll to Covid-19.

Italy's doctors, nurses and healthcare workers have been nominated for the 2021 Nobel Peace Prize in recognition of their efforts to face a very serious health emergency.

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