Disruptions of pharmaceutical supply in the COVID-19 global context

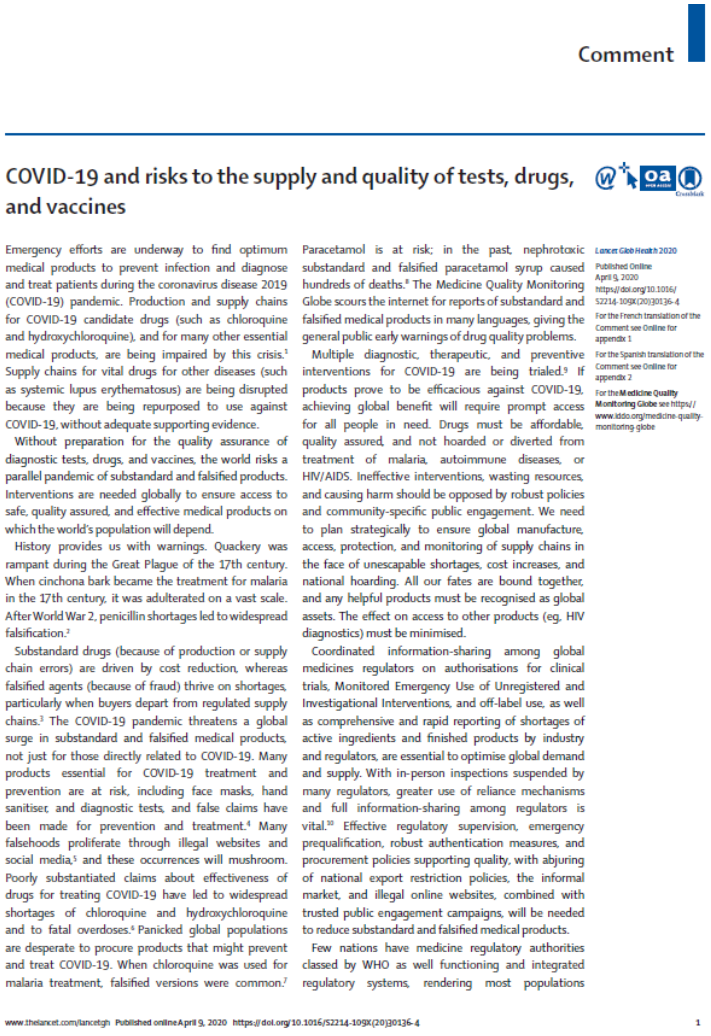
RAFFAELLA RAVINETTO

22 FEBRUARY 2021

What is impaired by this crisis?

- Health products for COVID-19
  - Vaccines
  - (Candidate) therapeutics
  - Diagnostics
  - Protective personal equipment's
- Many other essential health products

- Challenges to
  - Quality assurance
  - Supply & Availability
  - Efficacy and safety



COVID-19 and risks to the supply and quality of tests, drugs, and vaccines

Lancet Glob Health 2020
Published Online April 9, 2020 https://doi.org/10.1016/S2214-109X(20)30136-4

For the French translation of the Comment see Online for appendix 1

For the Spanish translation of the Comment see Online for appendix 2

For the **Medicine Quality Monitoring Globe** see https://www.iddo.org/medicine-quality-monitoring-globe

Emergency efforts are underway to find optimum medical products to prevent infection and diagnose and treat patients during the coronavirus disease 2019 (COVID-19) pandemic. Production and supply chains for COVID-19 candidate drugs (such as chloroquine and hydroxychloroquine), and for many other essential medical products, are being impaired by this crisis.[1] Supply chains for vital drugs for other diseases (such as systemic lupus erythematosus) are being disrupted because they are being repurposed to use against COVID-19, without adequate supporting evidence.

Without preparation for the quality assurance of diagnostic tests, drugs, and vaccines, the world risks a parallel pandemic of substandard and falsified products. Interventions are needed globally to ensure access to safe, quality assured, and effective medical products on which the world's population will depend.

History provides us with warnings. Quackery was rampant during the Great Plague of the 17th century. When cinchona bark became the treatment for malaria in the 17th century, it was adulterated on a vast scale. After World War 2, penicillin shortages led to widespread falsification.[2]

Substandard drugs (because of production or supply chain errors) are driven by cost reduction, whereas falsified agents (because of fraud) thrive on shortages, particularly when buyers depart from regulated supply chains.[3] The COVID-19 pandemic threatens a global surge in substandard and falsified medical products, not just for those directly related to COVID-19. Many products essential for COVID-19 treatment and prevention are at risk, including face masks, hand sanitiser, and diagnostic tests, and false claims have been made for prevention and treatment.[4] Many falsehoods proliferate through illegal websites and social media,[5] and these occurrences will mushroom. Poorly substantiated claims about effectiveness of drugs for treating COVID-19 have led to widespread shortages of chloroquine and hydroxychloroquine and to fatal overdoses.[6] Panicked global populations are desperate to procure products that might prevent and treat COVID-19. When chloroquine was used for malaria treatment, falsified versions were common.[7] Paracetamol is at risk; in the past, nephrotoxic substandard and falsified paracetamol syrup caused hundreds of deaths.[8] The Medicine Quality Monitoring Globe scours the internet for reports of substandard and falsified medical products in many languages, giving the general public early warnings of drug quality problems.

Multiple diagnostic, therapeutic, and preventive interventions for COVID-19 are being trialed.[9] If products prove to be efficacious against COVID-19, achieving global benefit will require prompt access for all people in need. Drugs must be affordable, quality assured, and not hoarded or diverted from treatment of malaria, autoimmune diseases, or HIV/AIDS. Ineffective interventions, wasting resources, and causing harm should be opposed by robust policies and community-specific public engagement. We need to plan strategically to ensure global manufacture, access, protection, and monitoring of supply chains in the face of unescapable shortages, cost increases, and national hoarding. All our fates are bound together, and any helpful products must be recognised as global assets. The effect on access to other products (eg, HIV diagnostics) must be minimised.

Coordinated information-sharing among global medicines regulators on authorisations for clinical trials, Monitored Emergency Use of Unregistered and Investigational Interventions, and off-label use, as well as comprehensive and rapid reporting of shortages of active ingredients and finished products by industry and regulators, are essential to optimise global demand and supply. With in-person inspections suspended by many regulators, greater use of reliance mechanisms and full information-sharing among regulators is vital.[10] Effective regulatory supervision, emergency prequalification, robust authentication measures, and procurement policies supporting quality, with abjuring of national export restriction policies, the informal market, and illegal online websites, combined with trusted public engagement campaigns, will be needed to reduce substandard and falsified medical products.

Few nations have medicine regulatory authorities classed by WHO as well functioning and integrated regulatory systems, rendering most populations

Newton PN, Bond K, on behalf of 53 signatories. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. Lancet GH 2020; published online April 9, 2020. https://doi.org/10.1016/S2214-109X(20)30136-4

1/3 Challenges to Quality Assurance

- **Medical Product Quality Report COVID-19** (Medicine Quality Research Group, Centre of Tropical Medicine & Global Health, University of Oxford)
- Under the radar
  - Vaccines
  - (Candidate) therapeutics
  - Diagnostics
  - Protective personal equipment's
  - Sanitizers and disinfectants
- Excerpta from December issue
  - … incidents with diverted, substandard or falsified COVID-19 supplies … we report on 37 alerts
  - Falsified/diverted vaccines in South Africa, Brazil and Philippines
  - Vaccines offered on Dark Web
  - Fewer articles on SF diagnostics but incidents do continue….
  - New cases of ethanol contamination of sanitizers
  - Frequent reports on SF PPE, often destined for health care workers

https://www.iddo.org/mq/research/medical-product-quality-reports

1/3 Challenges to Quality Assurance

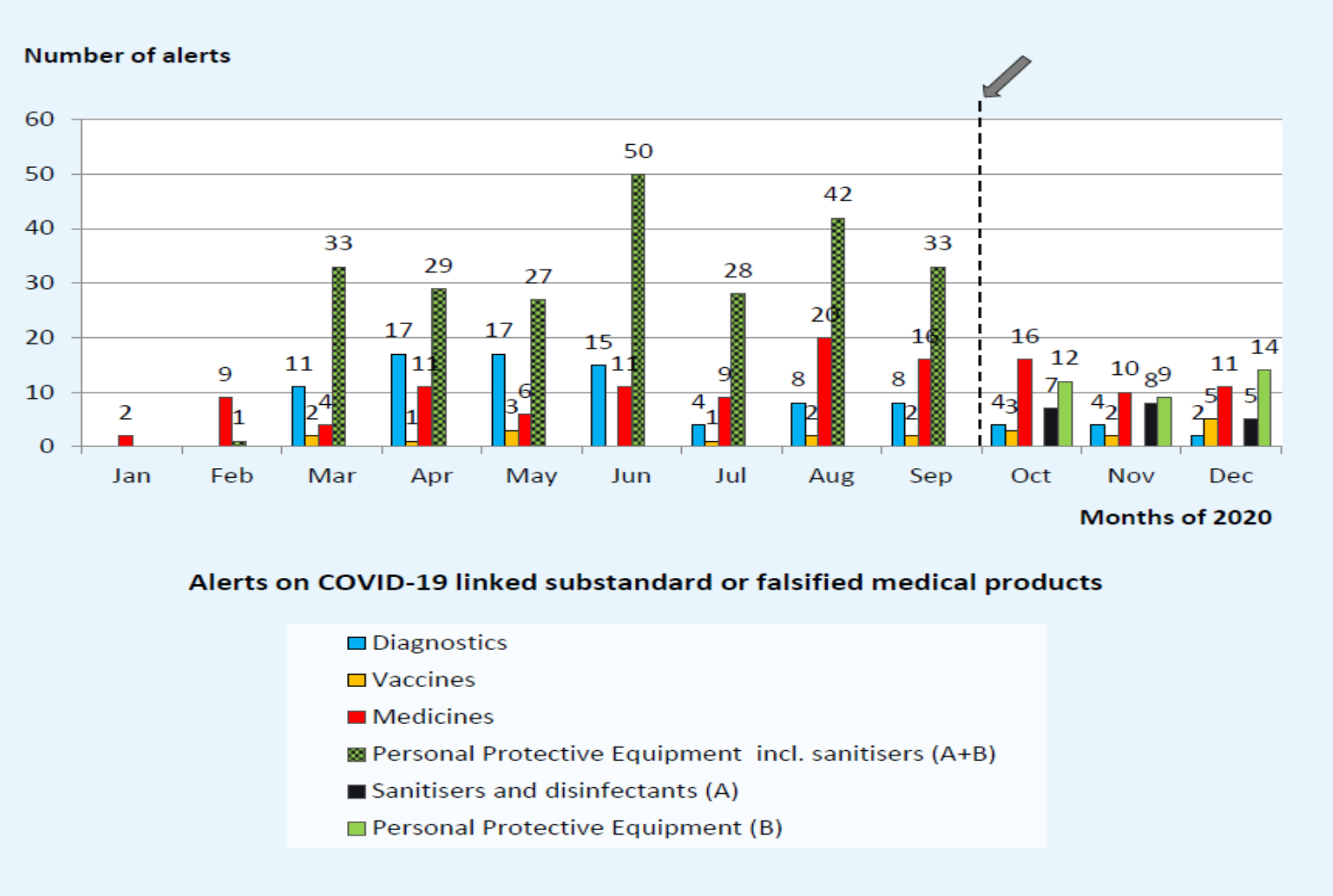


Figure 2. Number of alerts on the Medicines Quality Monitoring Globe by category of products and by mon

https://www.iddo.org/mq/research/medical-product-quality-reports

2/3 Challenges to Supply & Availability (all essential products)

- Continuous supply: critical for robust health systems
- The pandemic: disruptions in global supply chains
- The case of Nigeria:
  - " …. global lockdown, decreased manufacturing, unaddressed regulatory affairs, poor access by the population, lack of buffer stocks, security instability, poor funding of the healthcare system"
- The case of Rwanda:
  - "limited importation from abroad, and the panic buying practice among the customers and some institutions when responding to the pandemic".

Faiva et al. Drug supply shortage in Nigeria during COVID-19: efforts and challenges JPPP (2021) 14:17
Uwizeyimana et al. Drug supply situation in Rwanda during COVID-19: issues, efforts and challenges JPPP (2021) 14:12

2/3 Challenges to Supply & Availability (all essential products)

- Regulatory systems are critical to ensure access to safe and effective medicines before, during and after the pandemic
- Regulatory strengthening measures needed during the pandemic can and should enhance regulatory systems beyond it
- Suggestions to invest in local production:
  - Long term plans?
  - Framed into regional collaboration (i.e., “regional”, not “local” production)?
  - Framed in regulatory harmonization?

Commentary

BMJ Global Health

Strengthening regulatory systems for medicines in a changed world: where do we go from here?

Julie O'Brien [1], Rebecca Lumsden,[2] Judith Macdonald[2]

To cite: O'Brien J, Lumsden R, Macdonald J. Strengthening regulatory systems for medicines in a changed world: where do we go from here? *BMJ Global Health* 2021;6:e004680. doi:10.1136/bmjgh-2020-004680

Received 7 December 2020
Revised 9 December 2020
Accepted 11 December 2020

[1]Global Regulatory Policy and Intelligence, Global Regulatory Affairs, Pfizer Healthcare Ireland, Dublin, Ireland
[2]Global Regulatory Policy and Intelligence, Global Regulatory Affairs, Pfizer Ltd, Tadworth, UK

Correspondence to
Dr Julie O'Brien;
julie.obrien@pfizer.com

INTRODUCTION

National regulatory authorities (NRAs) play a vital role in the regulation of medicines globally. A diverse spectrum of NRAs exists, from those with less well-developed systems to those with well-established, advanced systems. Over the past several decades, great strides have been made to strengthen regulatory systems across the globe. For example, greater harmonisation of technical standards via The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[1] adoption of WHO initiatives such as Good Regulatory Practices[2] and the Global Benchmarking Tool,[3] greater use of digital tools and more international cooperation and collaboration–including regulatory reliance mechanisms—between regulatory authorities. These initiatives are essential because strong regulatory systems streamline the regulatory review and approval process, facilitating access to safe and effective medicines to patients.[4] Never has this endeavour felt more critical.

In December 2019, the first reports of a new virus began to emerge. Since then, over 60 million people globally have been infected with SARS-CoV-2, and over 1.4 million people have died to date due to COVID-19.[4 5] The full societal, cultural, economic and long-term physical and mental health impacts of this pandemic remain untold. As the pandemic has unfolded, the need for effective and efficient regulatory systems globally has never been more important. This is true both to ensure continued supply of existing critical medicines, such as those needed for severely ill patients with COVID-19, for example, anaesthetics, sedatives, anti-infectives, neuromuscular blockers and vasopressors, as well as for streamlined review and approval of new innovative medicines (including but not limited to potential COVID-19 vaccines and treatments).

Summary box

- Strengthening regulatory systems for medicines in low-income and middle-income countries is critical to ensure fit for purpose, future-proofed and efficient regulatory systems that facilitate access to safe and effective medicines for patients; this holds true before, during and after the COVID-19 pandemic.
- The COVID-19 pandemic has shone a light on weaknesses in regulatory systems around the globe, such as lack of digital adoption, and has precipitated the implementation of long-term aspirations for regulatory strengthening.
- National Regulatory Authorities around the world have demonstrated an extraordinary ability to adapt, including implementation of new ways of working, to fulfil their role both in relation to continued supply of existing critical medicines and review and approval of new innovative medicines (including but not limited to potential COVID-19 vaccines and treatments).
- Regulatory strengthening measures implemented during the COVID-19 pandemic can enhance regulatory systems more broadly beyond the current health emergency.

The multilayered challenges posed by the pandemic to regulatory systems around the world compel all stakeholders to reflect on how, collectively, we can build on the progress to date to strengthen key areas. Stronger regulatory systems will positively impact all stakeholders, during this pandemic and beyond. While there is no doubt that the COVID-19 pandemic is, so far, the most urgent health emergency of our time, the wider perspective of existing unmet medical needs beyond COVID-19 globally cannot be forgotten. Notably, the WHO's sustainable development goal (SDG) of '*one billion more people enjoying better health and well-being*' illustrates this, tracked via 14 SDG indicators as part of the WHO's Thirteenth General Programme of Work.[6]

We have previously published our view on what we believe to be the key pillars of

O'Brien J, Lumsden R, Macdonald J. Strengthening regulatory systems for medicines in a changed world: where do we go from here?*BMJ Global Health* 2021;6:e004680.

2/3 Challenges to Supply & Availability (HIV, malaria, tuberculosis)

- Deaths due to HIV, TB, malaria over 5 years could increase by up to 10%, 20%, and 36% respectively
- HIV: interruption of therapy, due to high health system demand
- TB: reductions in timely diagnosis/treatment, due to prolonged suppression of interventions
- Malaria: interruption of net campaigns

Articles

Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study

Alexandra B Hogan*, Britta L Jewell*, Ellie Sherrard-Smith*, Juan F Vesga*, Oliver J Watson*, Charles Whittaker*, Arran Hamlet, Jennifer A Smith, Peter Winskill, Robert Verity, Marc Baguelin, John A Lees, Lilith K Whittles, Kylie E C Ainslie, Samir Bhatt, Adhiratha Boonyasiri, Nicholas F Brazeau, Lorenzo Cattarino, Laura V Cooper, Helen Coupland, Gina Cuomo-Dannenburg, Amy Dighe, Bimandra A Djaafara, Christl A Donnelly, Jeff W Eaton, Sabine L van Elsland, Richard G FitzJohn, Han Fu, Katy A M Gaythorpe, William Green, David J Haw, Sarah Hayes, Wes Hinsley, Natsuko Imai, Daniel J Laydon, Tara D Mangal, Thomas A Mellan, Swapnil Mishra, Gemma Nedjati-Gilani, Kris V Parag, Hayley A Thompson, H Juliette T Unwin, Michaela A C Vollmer, Caroline E Walters, Haowei Wang, Yuanrong Wang, Xiaoyue Xi, Neil M Ferguson, Lucy C Okell, Thomas S Churcher, Nimalan Arinaminpathy, Azra C Ghani, Patrick G T Walker, Timothy B Hallett

Summary

Background COVID-19 has the potential to cause substantial disruptions to health services, due to cases overburdening the health system or response measures limiting usual programmatic activities. We aimed to quantify the extent to which disruptions to services for HIV, tuberculosis, and malaria in low-income and middle-income countries with high burdens of these diseases could lead to additional loss of life over the next 5 years.

Methods Assuming a basic reproduction number of 3·0, we constructed four scenarios for possible responses to the COVID-19 pandemic: no action, mitigation for 6 months, suppression for 2 months, or suppression for 1 year. We used established transmission models of HIV, tuberculosis, and malaria to estimate the additional impact on health that could be caused in selected settings, either due to COVID-19 interventions limiting activities, or due to the high demand on the health system due to the COVID-19 pandemic.

Findings In high-burden settings, deaths due to HIV, tuberculosis, and malaria over 5 years could increase by up to 10%, 20%, and 36%, respectively, compared with if there was no COVID-19 pandemic. The greatest impact on HIV was estimated to be from interruption to antiretroviral therapy, which could occur during a period of high health system demand. For tuberculosis, the greatest impact would be from reductions in timely diagnosis and treatment of new cases, which could result from any prolonged period of COVID-19 suppression interventions. The greatest impact on malaria burden could be as a result of interruption of planned net campaigns. These disruptions could lead to a loss of life-years over 5 years that is of the same order of magnitude as the direct impact from COVID-19 in places with a high burden of malaria and large HIV and tuberculosis epidemics.

Interpretation Maintaining the most critical prevention activities and health-care services for HIV, tuberculosis, and malaria could substantially reduce the overall impact of the COVID-19 pandemic.

Funding Bill & Melinda Gates Foundation, Wellcome Trust, UK Department for International Development, and Medical Research Council.

Introduction

The COVID-19 pandemic, and actions taken in response to it, will have far-reaching consequences on other diseases, poverty, food security, and economic growth.[1] In low-income and middle-income countries, a particular concern is the potential impact on three major health priorities, specifically, HIV, tuberculosis, and malaria, due to a possible disruption to health services. Many low-income and middle-income countries have high burdens of these three diseases, and millions of people depend on large-scale programmes to control and treat them.[2–4] In recent years, substantial progress has been made in reducing the burden of HIV, tuberculosis, and malaria, and ambitious targets have been set for reaching very low levels of burden by 2030, as part of the Sustainable Development Goals.[5] Interruptions to control programmes could result in major setbacks, compounding the direct impact of COVID-19.

We conceptualise the potential impact on HIV, tuberculosis, and malaria programmes as arising predominantly from disruptions to the usual activities and services due to COVID-19. These disruptions include mitigation strategies being undertaken in response to the COVID-19 pandemic, leading to the scaling back of certain activities and care-seeking; reduced capabilities of the health system due to overwhelmingly high demand for the care of patients with COVID-19; and interruptions

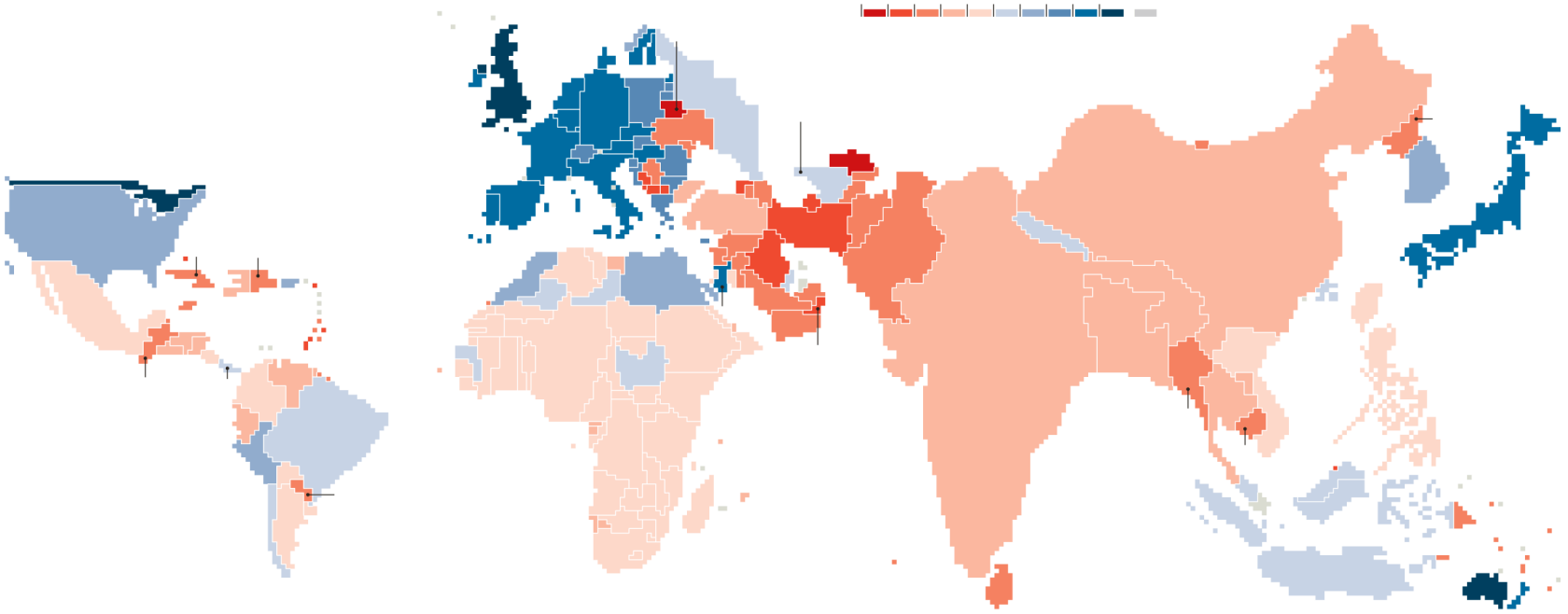
Lancet Glob Health 2020
Published Online July 13, 2020 https://doi.org/10.1016/S2214-109X(20)30288-6
See Online/Comment https://doi.org/10.1016/S2214-109X(20)30312-X

*Contributed equally
Medical Research Council Centre for Global Infectious Disease Analysis, Abdul Latif Jameel Institute for Disease and Emergency Analytics, Imperial College London, London, UK
(A B Hogan PhD, B L Jewell PhD, E Sherrard-Smith PhD, J F Vesga PhD, O J Watson PhD, C Whittaker MSc, A Hamlet PhD, J A Smith DPhil, P Winskill PhD, R Verity PhD, M Baguelin PhD, J A Lees PhD, L K Whittles PhD, K E C Ainslie PhD, S Bhatt DPhil, A Boonyasiri MD, N F Brazeau PhD, L Cattarino PhD, L V Cooper MPH, H Coupland MRes, G Cuomo-Dannenburg MMath, A Dighe MRes, B A Djaafara MRes, Prof C A Donnelly ScD, J W Eaton PhD, S L van Elsland PhD, R G FitzJohn PhD, H Fu PhD, K A M Gaythorpe PhD, W Green MRes, D J Haw PhD, S Hayes MSc, W Hinsley PhD, N Imai PhD, D J Laydon PhD, T D Mangal PhD, T A Mellan PhD, S Mishra PhD, G Nedjati-Gilani PhD, K V Parag PhD, H A Thompson MPH, H J T Unwin PhD, M A C Vollmer PhD, C E Walters PhD, H Wang M Sc, Y Wang, X Xi M Sc, Prof N M Ferguson DPhil, L C Okell PhD, T S Churcher PhD, N Arinaminpathy DPhil, Prof A C Ghani PhD, P G T Walker PhD,

Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in LMICs: a modelling study. Lancet Glob Health 2020. Published Online July 13, 2020. https://doi.org/10.1016/S2214-109X(20)30288-6

2/3 Challenges to Supply & Availability (the case of vaccines)

- Based on public data on premarket purchase agreements, high income countries reserved more than half of vaccine doses despite being 14% of the world's population



The Economist: https://www.economist.com/graphic-detail/2021/02/13/there-will-be-enough-vaccines-for-all-if-rich-countries-share

Kuehn BM. HICs Have Secured the Bulk of COVID-19 Vaccines. *JAMA.* 2021;325(7):612

3/3 Challenges to Efficacy and safety

- Different key-stakeholders displayed rushed decisions and lapses in judgment in handling chloroquine/hydroxychloroquine as potential COVID-19 therapeutics and prophylactics
- Lessons for how the guardians of regulation and public health can inadvertently damage public trust.
- How to balance the urgency of new/repurposed medicines vs the need of an in-depth assessment?

Singh and Ravinetto *Journal of Pharmaceutical Policy and Practice* (2020) 13:47
https://doi.org/10.1186/s40545-020-00244-0

Journal of Pharmaceutical Policy and Practice

COMMENTARY Open Access

COVID-19 therapeutics: how to sow confusion and break public trust during international public health emergencies

Jerome Amir Singh[1*] and Rafaella Ravinetto[2]

Abstract

Since SARS-CoV2 was declared a *Public Health Emergency of International Concern*, those tasked with the stewardship of public health at a global, regional, and local level—policymakers, politicians, scientists, drug regulators, health officials, professional associations, journal editors, publishers, and clinicians—have displayed rushed decisions and lapses in judgment in their handling of chloroquine and hydroxychloroquine as potential COVID-19 therapeutics and prophylactics. These lapses merit noting as they hold lessons for how the guardians of medicines regulation and public health can inadvertently sow confusion and damage public trust.

Background

The novel coronavirus SARS-CoV-2 represents a significant and urgent threat to global health. With the global tally of infected people now numbering in the millions, and the number of people who have succumbed to the disease now quantified in the hundreds of thousands, the identification of efficacious SARS CoV-2 therapeutic candidates has quickly become one of the world's most pressing health needs. Since SARS-CoV2 was declared a *Public Health Emergency of International Concern*, those tasked with the stewardship of public health at a global, regional, and local level—drug regulators, policymakers, politicians, scientists, health officials, professional associations, journal editors, publishers, and clinicians—have displayed rushed decisions and lapses in judgment in their handling of chloroquine (CQ) and hydroxychloroquine (HCQ) as potential COVID-19 therapeutics and prophylactics. These lapses merit noting as they hold lessons for how the guardians of medicines regulation and public health can inadvertently sow confusion and damage public trust. Such outcomes are antithetical to what the world needs when it is confronting a serious public health emergency of international concern.

A review of key global developments on CQ and HCQ in the context of COVID-19

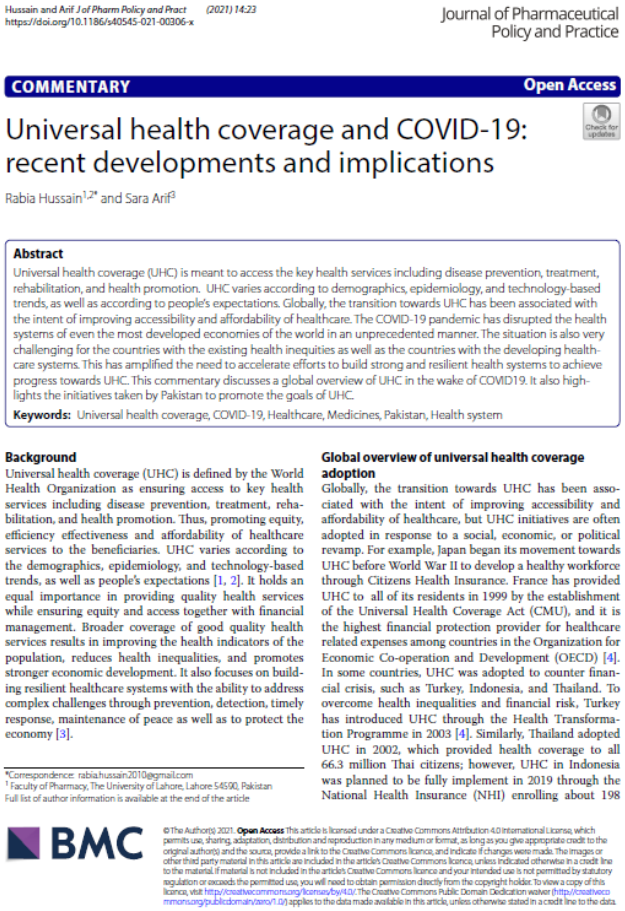
In February 2020, Chinese scientists reported that CQ had demonstrated apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multi-centre clinical trials conducted in China [1]. On 13 March 2020, the WHO published interim guidance for the management of COVID-19 [2]. The guidance contained no recommendation in regard to CQ or HCQ. On 16 March 2020, a French researcher announced early results of an open-label, single-group study that involved contemporaneous, but nonrandomized controls, which indicated that HCQ treatment was significantly associated with viral load reduction in COVID-19 patients, and the results were published days later in the *International Journal of Antimicrobial Agents* (*IJAA*) [3, 4]. On 18 March 2020, to expedite the identification of efficacious candidate agents, the WHO and partners launched the 'Solidarity Trial', an international randomised clinical trial designed to compare four treatment options for hospitalised patients—remdesivir; lopinavir/ritonavir; lopinavir/ritonavir with interferon beta-1a; and CQ or HCQ—against standard of care, to assess their relative effectiveness against COVID-19 [5]. On 19

* Correspondence: singhj@ukzn.ac.za
[1]Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa
Full list of author information is available at the end of the article

Singh, J.A., Ravinetto, R. COVID-19 therapeutics: how to sow confusion and break public trust during international public health emergencies. J Pharm Policy Practice 2020; 13: 47

The way forward

- Transition towards Universal health coverage (UHC) is associated with the intent of improving accessibility and affordability of healthcare
- COVID19 disrupted *all* health systems, in an unprecedented manner
- Biggest challenges are for countries with health inequities or developing health systems
- COVID19 amplified the need to accelerate efforts to build resilient health systems towards UHC



Hussain and Arif J of Pharm Policy and Pract (2021) 14:23
https://doi.org/10.1186/s40545-021-00306-x

Journal of Pharmaceutical Policy and Practice

COMMENTARY Open Access

Universal health coverage and COVID-19: recent developments and implications

Rabia Hussain[1,2*] and Sara Arif[3]

Abstract

Universal health coverage (UHC) is meant to access the key health services including disease prevention, treatment, rehabilitation, and health promotion. UHC varies according to demographics, epidemiology, and technology-based trends, as well as according to people's expectations. Globally, the transition towards UHC has been associated with the intent of improving accessibility and affordability of healthcare. The COVID-19 pandemic has disrupted the health systems of even the most developed economies of the world in an unprecedented manner. The situation is also very challenging for the countries with the existing health inequities as well as the countries with the developing health-care systems. This has amplified the need to accelerate efforts to build strong and resilient health systems to achieve progress towards UHC. This commentary discusses a global overview of UHC in the wake of COVID19. It also highlights the initiatives taken by Pakistan to promote the goals of UHC.

Keywords: Universal health coverage, COVID-19, Healthcare, Medicines, Pakistan, Health system

Background

Universal health coverage (UHC) is defined by the World Health Organization as ensuring access to key health services including disease prevention, treatment, rehabilitation, and health promotion. Thus, promoting equity, efficiency effectiveness and affordability of healthcare services to the beneficiaries. UHC varies according to the demographics, epidemiology, and technology-based trends, as well as people's expectations [1, 2]. It holds an equal importance in providing quality health services while ensuring equity and access together with financial management. Broader coverage of good quality health services results in improving the health indicators of the population, reduces health inequalities, and promotes stronger economic development. It also focuses on building resilient healthcare systems with the ability to address complex challenges through prevention, detection, timely response, maintenance of peace as well as to protect the economy [3].

*Correspondence: rabia.hussain2010@gmail.com
[1] Faculty of Pharmacy, The University of Lahore, Lahore 54590, Pakistan
Full list of author information is available at the end of the article

Global overview of universal health coverage adoption

Globally, the transition towards UHC has been associated with the intent of improving accessibility and affordability of healthcare, but UHC initiatives are often adopted in response to a social, economic, or political revamp. For example, Japan began its movement towards UHC before World War II to develop a healthy workforce through Citizens Health Insurance. France has provided UHC to all of its residents in 1999 by the establishment of the Universal Health Coverage Act (CMU), and it is the highest financial protection provider for healthcare related expenses among countries in the Organization for Economic Co-operation and Development (OECD) [4]. In some countries, UHC was adopted to counter financial crisis, such as Turkey, Indonesia, and Thailand. To overcome health inequalities and financial risk, Turkey has introduced UHC through the Health Transformation Programme in 2003 [4]. Similarly, Thailand adopted UHC in 2002, which provided health coverage to all 66.3 million Thai citizens; however, UHC in Indonesia was planned to be fully implement in 2019 through the National Health Insurance (NHI) enrolling about 198

- *Hussain R, Arif S. Universal health coverage and COVID-19: recent developments and implications. J Pharm Policy and Pract (2021) 14:23*

Raffaella Ravinetto

Public Health Department

rravinetto@itg.be