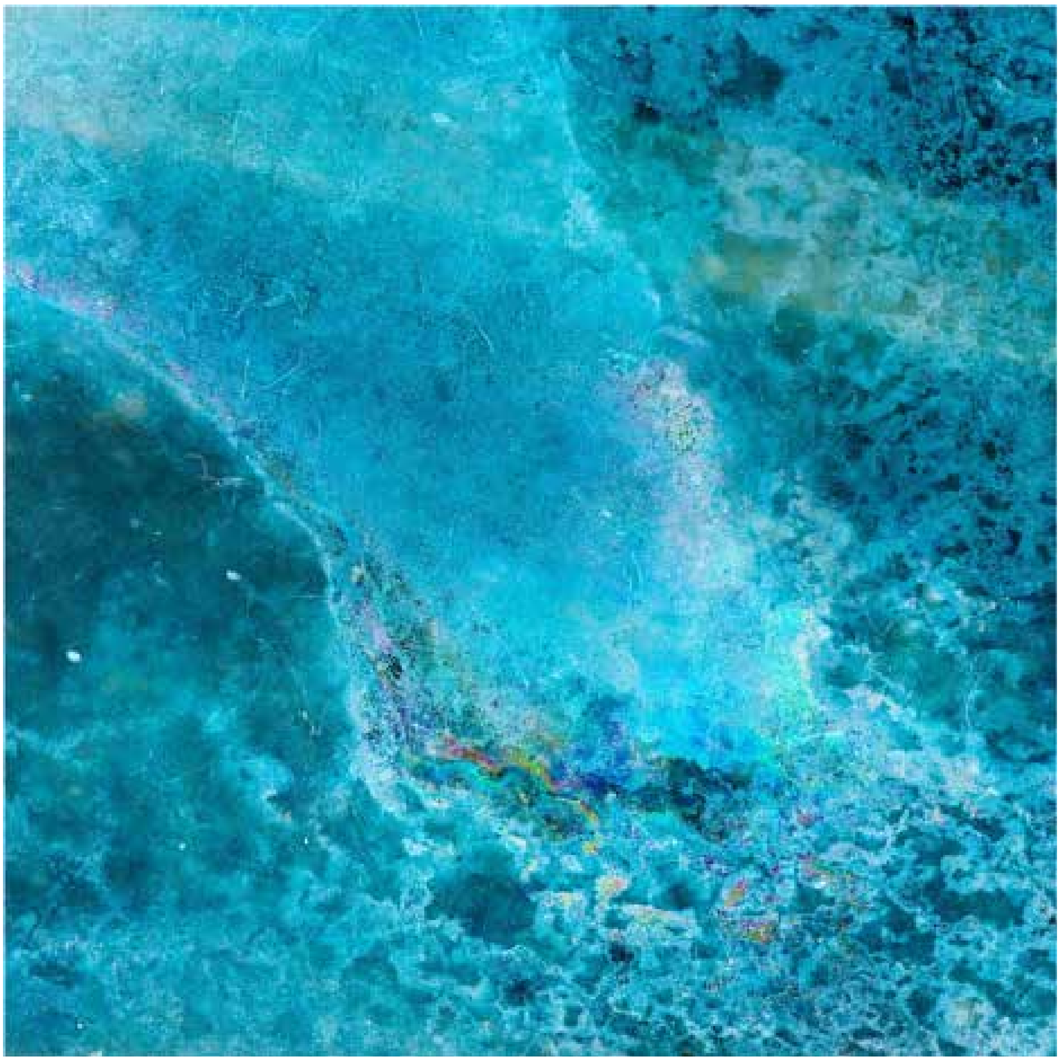
AMR & THE ENVIRONMENT A GLOBAL & ONE HEALTH SECURITY ISSUE



THINK-DO-TANK AMR GENEVA INTERNATIONAL

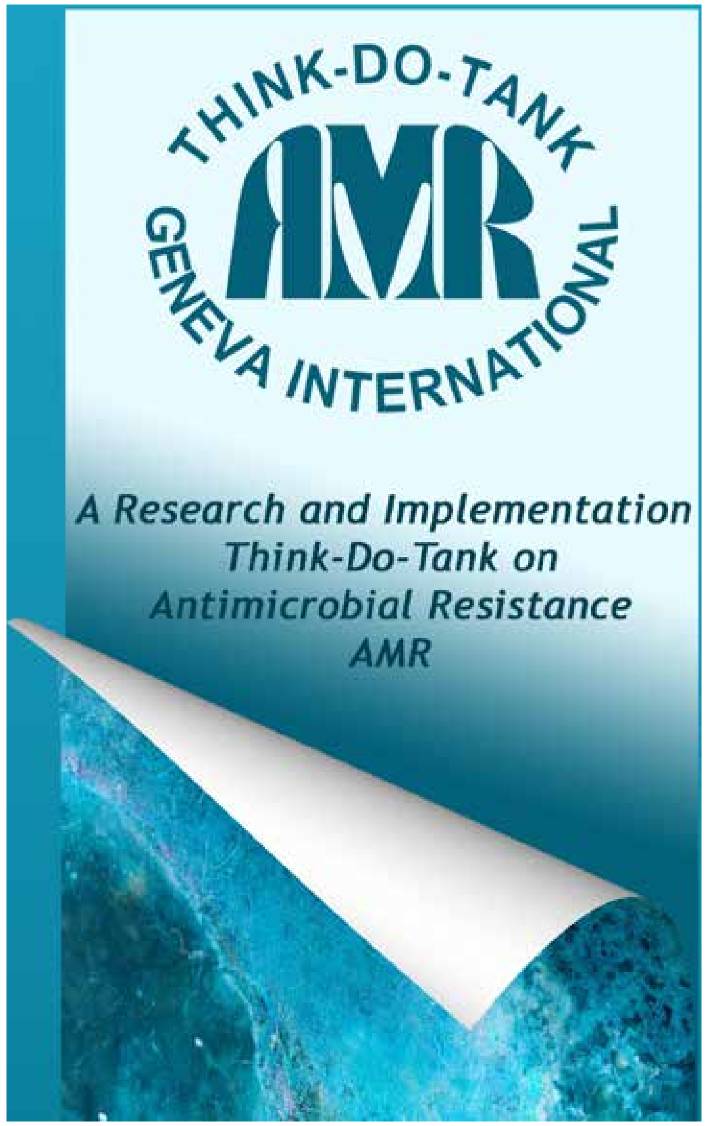
"AQUA STELLA" from Natural Abstractions by artist photographer Marcel Crozet

AMR & THE ENVIRONMENT

A Global & One Health Security Issue

Director of Publication & Editor in Chief:
Garance F. Upham

A publication of the AMR Think-Do-Tank, Geneva International
Maison des Associations, Rue des Savoises 15,
1205 Geneva, Switzerland



ISSN 2673-9232

www.amrthinkdotank.org

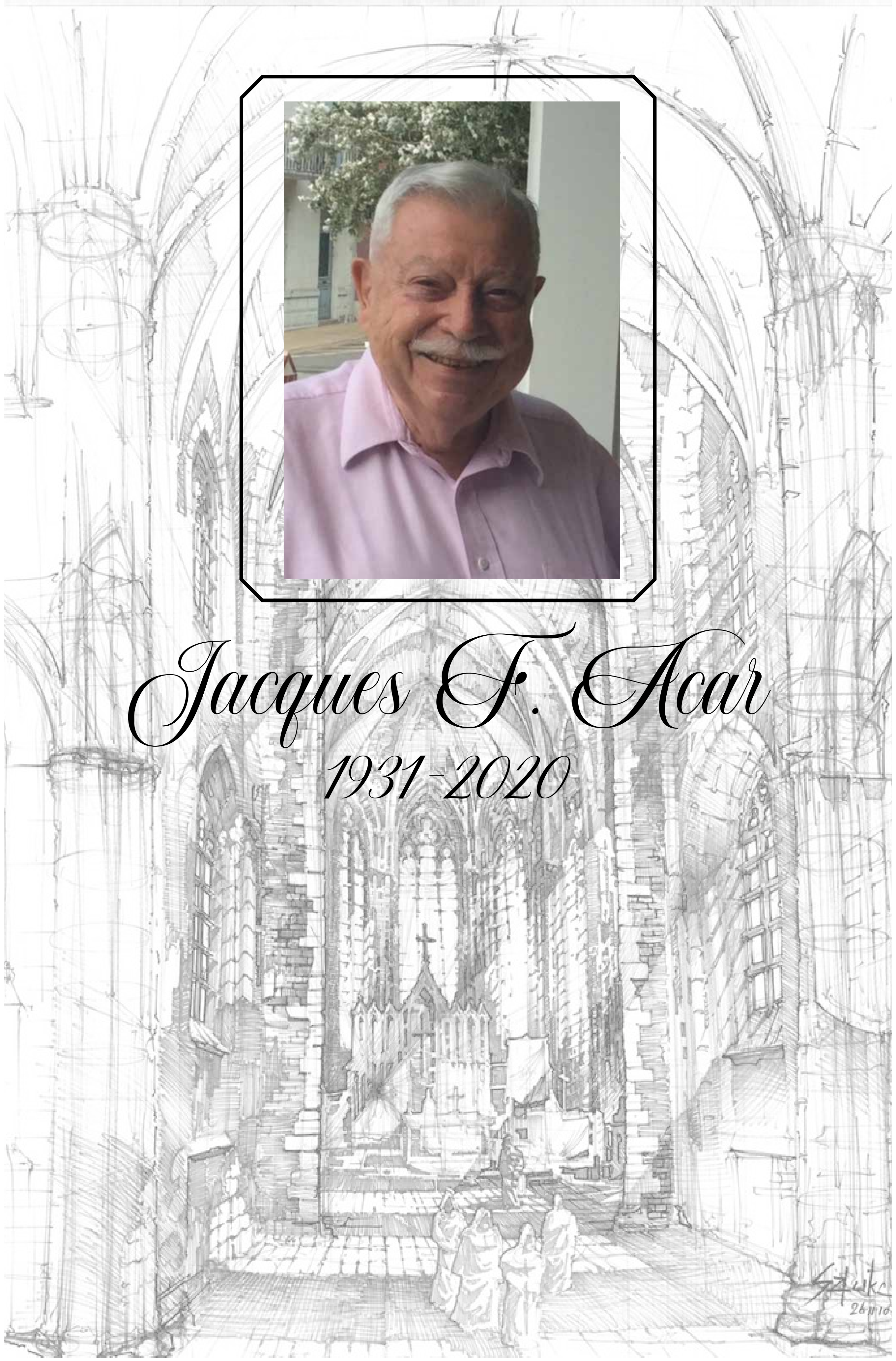
email: info@amrthinkdotank.org

132 pages; glossy paper, A4 format
Price: 79 CHF / 69 euros
Reduced prices for LMICs - email us

TABLE OF CONTENT

We would especially like to thank :
Cover : “Aqua Stella”, by Natural Abstraction Photographer, Marcel Crozet, France
Logo AMR Think-Do-Tank : by artist Karen Kabaskalyan, Armenia
Section introduction - Portrait Jacques Acar - Credit: Acar’s family
Table of Content: Alpine Geneva Above the Clouds - Credit: Carine Trioux
Section I, Miro Fountain, Fondation Maeght, France - Credit: Dominique Thierry
Section II, Marine Farm of Noirmoutier - Credit: Hemarina SA, France
Section III, Leaf on wood - Credit Thomas Schwarz
Section IV, Door and Clouds - Credit: Thomas Schwarz
Section V, Autumn Leaves -Credit: Thomas Schwarz
Section VI, Hand Washing Street System - Anonymous, Conakry, Guinea.
Section VII, In the Swiss Grisons, 17th Century Church, Alpes behind Geneva - Credit: Thomas Schwarz
Editors: Arno Germond, PhD, researcher, Japan & France; Garance Upham, Editor in Chief
Design, graphics, layout: Natasha Frank, Jean-Jacques Monot.

The opinions expressed in each article are the sole responsibility of its authors and do not engage the board of the publication, nor the AMR Think-Do-Tank; Geneva International. Debates of ideas are the firewood of a live participatory State. We believe in diversity and freedom of opinions.



Obituary : Jacques F. Acar (1931-2020)

For almost 20 years, when the phone rang a single word was enough for me to recognize Jacques Acar, “Allo!”. His recognizable baritone voice conveyed the warmth of his generosity of heart and the depth of his thought. It was always a pleasant surprise and often the point of the call was to find a time to have dinner together. I had the chance to meet him thanks to our activities within the French Society of Microbiology as part of the organization in Paris of the international congress bringing together the three divisions of the International Union of Microbiological Societies (IUMS) entitled “The world of microbes” in the summer of 2002. It was the first time in decades that the three divisions of the IUMS had held their world congress together, bringing together bacteriologists, virologists and mycologists. We were both on the organizing committee. When I first heard him at a meeting of the committee, his voice captured my attention as well as everyone else’s, and the clarity and correctness of his words impressed me. It was around this time that I discovered who he was: a great medical microbiologist. His brilliant career was excellently described in the article published in his memory in the journal Clinical Microbiology and Infection, of which he was the first editor in chief[1].

Sometime before that congress, we became friends by chance. We ended up on the same plane on our way to a conference in San Francisco. We met at boarding and talked a lot during the flight and found out that we were both studying classical Arabic. This was one of our first topics of non-scientific conversation. The following Christmas, Jacques Acar gave me the CD of Christmas songs sung by Fairouz, which I still listen to from time to time as the winter holiday season approaches.

We often talked about science and human and veterinary medicine and his way of talking about bacteriology was fascinating and very informative for the virologist that I am. He had immense knowledge and a curious and lively mind which also prompted him to take an interest in other disciplines such as mine. Concerned about the danger of the rise in antimicrobial resistance, which he was following closely, Jacques Acar had, before others, a “One Health” vision of the subject encompassing the analysis of this phenomenon both in humans and animals.

We also often talked about other things because his curiosity of mind went beyond science. He was cultured and had a passion for music and for singing. An opera enthusiast, he was an assiduous spectator but also a dedicated practitioner of the lyric art he had a voice for. We also talked about our personal lives but also about everything and nothing with laughter and good humor during our friendly dinners. Jacques Acar was full of life and energy despite his advancing age. His disappearance due to COVID-19 froze the blood of all those who loved and admired him, it is a great misfortune. My thoughts are with his family. He will never be forgotten.

Professor, Dr. Jean-Claude Manuguerra, Pasteur Institute,
Head, Expertise and Research Unit “Environment and infectious Risks”, Laboratory for Urgent Response to Biological Threats, and head, OIE (Organisation for Animal Health) Collaborating Center, the Detection and Identification in Humans of Emerging Animal Pathogens and Development of Tools for their Diagnosis.

(1) Cambau, E.; Gutmann, L.; Mainardi, J.-L.; Goldstein, F.; Buu-Hoi, A.; Collatz, E.; Poljak, M.; Kahlmeter, G.; Phillips, I.; Baquero, F. Jacques F. Acar (1931–2020). Clin. Microbiol. Infect. 2020, 26 (9), 1261–1263. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30337-2/fulltext

Garance Upham, left, sitting next to Jacques Acar, during an evening event of the AGISAR/WHO group to honor Professor Awa Aidara Kane.

WHAT'S EXCITING ABOUT A THINK TANK?

The joy of creating an entity with Jacques Acar and the sorrow upon losing him.

Garance Upham

The joy of creating an entity with Jacques Acar and the sorrow upon losing him.

Coming and going between old Europe and America: there used to be, in the United States, a lively mindset allowing a person to switch entirely work, habits, constrains, with a wish to swim in new waters. Today, perhaps, decades later, this athletic way of thinking is more lasting in immigrant youth to adventurous countries in Asia, Australia. But Jacques and I had shared that experience of constant back and forth. The late Dr. Jacques Acar had felt the American call in his young adult years, and bridging science across the oceans and the seas had been a thread in his life as a researcher, a clinician, a maverick builder of scientific societies and varied endeavors, from his co-founding of ISID, the International Society on Infectious Diseases, or ESMID the European Society for Infectious Diseases and Microbiology, or APUA, the Alliance for the Prudent Use of Antibiotics, to his key input in AGISAR, the Advisory Group on Integrated Surveillance of Antimicrobial Resistance of the WHO, his expertise to the OIE, then the Fleming Fund, or one of his very last life initiatives in building the AMR Think-Do-Tank, Geneva International, with us.

Born in Senegal of Lebanese parents, he had a wide scientific, musical, historical, and medical culture with an American-like doer attitude, this without the pettiness of the social ladder climber: he did not care to assert authority or dominance on others nor would he choose friends or company based on society's judgment, caste or class.

At 88, Jacques was, more than ever, a remarkable thinker and doer. We had met initially in the hallways of the RICAI congress in Paris, several years ago. It was to be the beginning of a fabulous friendship. I really loved that man, and my hubby, computer engineer and mathematician, partook of Jacques' delight for good company and dislike for appearances at the expense of real science. In Paris, Geneva or elsewhere, the three of us had constant hours-long passionate discussions, and him and I were always sending each other messages on Whatsapp when not on the telephone.

IN THE TRADITION OF CHARLES NICOLLE

The great scientist Charles Nicolle used to say: "*Je déteste les expériences pour voir, j'aime les expériences pour penser*", (I hate experiments just in case - for 'chance', I love experiments to think). Nicolle, an early days Pasteur adventurer, had identified the flea as the carrying agent of the great Typhus epidemic in Tunis, not through its bite, but indirectly, through the flea's dejection which enters the blood of the victim when the later scratch! Hence bums, accustomed to bites, not scratching, were not affected like the thousands of people dying in Tunis at the time. Acar always reminded me of Nicolle's investigative thinking, and of Dr. Charles Mérieux's, whom I had known well in the 1990s, a diplomat and a pioneer. Jacques Acar, with his half a century of work in antibiotic resistance, had warned: beware of too strict guidelines: as a doctor, you may be justified in prescribing antibiotics to an old person with the viral flu, because the fragility of the patient would be a frequent terrain for bacterial infection; be wary of not prescribing antibiotics for an African child with measles: the later viral disease rarely ever travel unaccompanied by a bacterial infection, he said: Think!

Jacques insisted: antibiotic resistance is constantly created by biocides, pesticides, chemicals, or metals, released into the environment. "Blaming" the individual patient or the MD or the veterinarian, or the small farmer, is not a policy. Taking a broader One Health approach is, yes.

The notion of live experimenting, or doing, or not just a cloud level set, but also getting your hands in the mud of day to day living and national or international policy-making, and looking deep into the origin and consequences of proposed policies.

> Q: A pioneer in AMR, your experience goes back over 50 years?
>
> **Jacques Acar: *I am wary of 'rabbit hunt' like initiatives on AMR. I am of the generation of Thomas O'Brien, now 88, who was the first to put together a hospital program for surveillance of antibiotic resistance in 1970, and it is with him that we brought concern for AMR in the World Health Organization.***
>
> ***My master was Yves Chabbert, then Chair for Bacteriology at the Pasteur Institute, the first national reference center for AMR in France. My first encounter with antibiotic resistance was in 1954 with a 21 years old German patient who had an endocarditis infection with Staphylococcus aureus. His infection was resistant to everything we had at the time, treated desperately with penicillin and streptomycin, he died within a few days.***
>
> *Interview Sept 2016, AMR-Times read it on : www.AMRThinkDoTank.org*

JACQUES ACAR AND COVID-19

Jacques Acar died of COVID-19 caught in our beloved USA, after a trip for scientific meetings. He died on March 27th, 2020, upon his return to Paris. He had written to me on WhatsApp stranded in America after the US Administration stopped air traffic with Europe: "*I am stuck here, waiting for news from Air France for my return flight, but I love walking on the beaches of Rhode Island, it is just a wonder, I am in no hurry!*", his last words to me. In these days of COVID-19, I like to quote an African saying: "When an elderly dies it is as if a library went up in flame" Jacques was more than a walking library, encyclopedia of knowledge on AMR, he was always ready to do somersaults trials in his understanding, as when struggling with a metagenomics congress in Geneva, or to challenge a government official by commenting that France was no longer training any microbiologist!

Today, 12th months into the pandemic, a US study shows "2.5 Million Person-Years of Life Have Been Lost Due to COVID-19 in the United States alone". Shamefully it has become frequent to hear "news" report and authoritative 'experts' reporting that COVID-19 kills "only the elderly", as if not significant, a telltale on which fools seize upon to claim the pandemic is just like seasonal flu, only affecting the near-dead, and a sort of myth, to refuse masks and confinements. Let us remember and pay tribute to the first world-known death from COVID-19: a young adult, only 34 years of age, the whistle-blower of Wuhan, China: Dr. Li Wenliang, an ophthalmologist. He died on Feb 7th, 2020, of COVID-19 caught treating a glaucoma patient a month earlier. After the fact, he was made a hero.

Today, like yesterday and the day before, many young working adults, 45,000 as of December 1rst, many health care workers, have lost their lives to COVID-19.

THE AMR THINK-DO-TANK

A brainstorming think tank is the mixing of widely different disciplines, ages, backgrounds, and experiences. And what's rewarding about a "Think Do Tank", what does the 'Do' signifies? Implementation Research, as introduced into TDR/WHO by one of our founding lady scientist, Jane Kengeya-Kayondo. To make it simple: a Deming cycle like Plan-Do-Check-Act type of research approach.

Jacques Acar thought that in AMR we must first think of "contagion", how is it transmitting in hospitals, in public places, or via the Environment? Wastewaters? In building air flows? *Among the innumerable stories he told me over the years: the MRSA staphylococci present in a patient open wound waiting in an ICU hallway for treatment, and the finding a few days later of that exact same bug in a hospitalized patient wound in a room opening on that hallway? They had had different carers, never been in the same room*. Acar needed no convincing on pathogens' travel via air flows. Jacques, rooted in the Middle East, with a foot in France, and one in America, embodied the best of the Western and Arab world. At 88 he was a passionate learner in economics, interested in understanding how vulture funds could damage a young antibiotic company. A great amuser of youth. An original to the core.

Dr. Jacques Acar had agreed to be our scientific chair, adding that he was leaving all the tedious administrative work to me, and so insisted I was to be president, even as he signed as co-president on the AMR Think-Do-Tank Statutes at our general assembly in September 2019.

Jacques took people as they were, without prejudice. He was neither ever dominating nor apt at being dominated. He enjoyed my athletic 'Circus like' imagination and did not treat me or view me as 'just a woman', and much less as just a 'polio'. Notwithstanding a general vaccine-induced four limbs paralysis in my first year in life, I had managed to walk, leaving corsets, crutches, braces, and orthopaedic shoes behind at age 13, just like Forrest Gump, after a childhood of paralympics like daily training and some great surgeries in the US then France, by a historic pioneer in pediatric orthopedics, Pr Merle d'Aubigné, walking well until my 60s. That was among the major difference of opinion between us, more than being 20 years apart: I loved sports, swimming, etc. I campaigned for including physiotherapy in Primary Health Care even. He hated exercices!

And we both advocated vaccinations for humans and animals. I had participated in the first meetings launch and advocacy of IAVI, the early 1990s effort at supporting R&D for an HIV vaccine.

To be able to walk, with 85% of muscles paralyzed, had demanded supple coordination between the mind's imagination and the body as a Moshe Feldenkreis, would grasp. Clearly, I was a wild circus animal, and remained so, with all the scars and holes of a survivor, but with an inordinate capacity for gymnastics of the mind, always searching for new ideas and trends in science or to pierce easily deep causes and motivations in policymakers.

Jacques and I had this in common of being seen as somehow "courageous" (a hateful epithet) for traveling worldwide to scientific meetings just for the fun for great debates, just for the mind's athletics.

He was a doctor with a real scientific mind set, always thinking through issues and challenges, and further had an extraordinary memory organized by years: he would say: 1959, yes, such and such took place, 1971, this drug came on the market, 1972, this and that happened. A scientific library of over 50 years of world events in medicine, drugs, science news, all well organized year by year as if on a shelf, in his head!

He was fascinating, the most lovable elderly man I ever encountered and befriended since the death of Dr Léon Lapeyssonnie or Dr Charles Mérieux, them too, great storytellers and world citizens, each a friend whom, after you met them, not once, but many times, you never could forget.

THE ATHLETICS OF THE MIND

Jacques Acar and I loved the brainstorming of ideas, the athletics of the mind, the search for causality.

COVID-19 killed him,
but our love for him is eternal
and my loss is forever.

EDITORIAL

Dr. Arno Germond

Antimicrobial resistance (AMR) has become one of the main health threats of our century, and the rise and the emergence of COVID-19 is likely seen as an aggravating factor of AMR due to its impact on the economy, the chain of supplies, and the increased use of drugs. A hundred AMR-related medical conditions, including cancer care and sepsis, are seen as a growing threat.
As a response, many institutions are currently promoting the development of novel drugs and vaccines through massive public investments campaigns and 'market push-pull' programs. However, while new tests and therapeutics are welcome, humanity will not eradicate these without emphasizing the much neglected systemic features of AMR.

To quote Prof. Tong Zhang, top Hong Kong, China world expert on AMR: "*The critical role of the environment in the dissemination of antibiotic resistance has become more and more obvious*". In the light of these considerations, an effective course of action against antimicrobial resistance must go beyond a naïve arm race opposing innovation in drug development and fast evolving pathogens.

The AMR Think-Do-Tank has been trying to highlight the overlooked yet fundamental aspects of AMR. We believe that addressing the symptomatic aspects of AMR will not solve the problem. In past decades, countless number of meetings and billions of dollars have been invested into the development of novel drugs, yet despite our ingenuity, no new class of antibiotic drug has been approved since.
On the other hand, we have seen a huge increase in the consumption of chemicals and drugs, while their release into the environment, creating antibiotic resistance, is a strong concern which is rarely addressed by governments and major institutions.

Thus, we strongly believe that "One Health and Global Health" approachs are to be adopted. Environmental issues, urban environment, monitoring of wastewater, are some of the essential aspects that we try to highlight, because crucial to prevent the spread of infectious diseases and resistant bacteria.
Arguably, the airborne spread COVID-19 clearly acted as a catalyst to address these important issues, thus we find it pertinent to talk about COVID-19 and AMR together in this edition. TB is an example of an airborne disease with increased AMR cases, yet little emphasis on airborne transmission issue.

This book is intended for policy makers to face and improve preparedness of drug-resistance and emerging pandemic. It does not pretend to be a consensus overview document - rather we prefer to give highlights of key out of the box topics, bridging into ecological, urban, or climate change standpoint, notably with a central piece on building pandemic preparedness. As highlighted in this book, "*The fundamental limitation we face is not lack-of-evidence, cost or access to technology, but the way the environment is viewed and prioritized by key actors across policy and practice communities in both the public and private sectors.*" (Williams and Jinks, Wellcome Trust).

The AMR-Think-Do-Tank has gathered here world experts to provide opinion pieces and study cases to highlight where progress has been made, but also to identify the remaining gaps. Through this book, you will find here the most up to date articles addressing the multidisciplinary aspects of the AMR and COVID issues, including but not limited to, better policies, building practices, safety management, educational policies, training of healthcare staff.
We thank all the contributing authors, and wish you a good reading.

Arno Germond has a PhD in system biology, he studies microbial systems using molecular biology, advanced spectral imaging and AI modellisation.
He worked in Japan for 12 years both in enterprises and academic institutions, including 6 years at RIKEN Laboratories where he led a team on antimicrobials resistance. Among other awards, Dr. Germond was awarded an Early Career Award in Biophysics in 2018. In his free time, Dr Germond is interested in solutions to develop resilient cities and societies.
Dr Germond is Vice-President, AMR Think-Do-Tank, Geneva International

ABOUT THIS EDITION

Garance Upham, Editor in Chief & Dr Arno Germond, Editor

Between the initial concept of a dossier for Policy Makers coming out of our participation in EDAR2019, The 5th International Symposium on the Environmental Dimension of Antibiotic Resistance, in June 2019, in Hong Kong, and today, a series of extraordinary events have, to say the least, shaken and overhauled this undertaking, with a turmoil of COVID-19 epidemics affecting our private and social lives, and the core of our project : the devastating deaths of Dr Acar, aged 88, and that of Dr Wenglian, aged 34. This edition, publicly announced by the AMR Think-Do-Tank on Feb 7th, at our first public event, in Geneva, went through very tumultuous waters.
EDAR5 had been chaired and organized by Prof. Tong Zhang - see articles this issue -- and Prof. Keiji Fukuda - formerly DG AMR at the WHO.

Feb 7th turned out to be a sad date with the death of Wuhan whistle-blower, Dr Li Wenglian, the 34 year old ophthalmologist, contaminated by a patient, while the WHO-EB began its public briefings on the coronavirus. A dossier on ***"Ophthalmology in AMR & Pandemics"*** *is among our projects.*

All but a few of the initial experts solicited were siphoned into domestic and global emergencies.
Then in September, we were spurred to relaunch with the prospect of an "*in person*" **World Health Assembly** (WHA) in Geneva's UN headquarters, privately planned by the WHO in early September. Yet, the WHA, and the following Executive Board meetings, became "virtual" as the epidemic struck back in waves. How to conceive a book for policy makers when the historical WHA has become a webinar behind a screen? A catastrophy in health democracy, compared with the mixing for ten days with thousands of participants: Ministers of Health,/ MoH's CEOs, Heads of R&D institutes, DG Health, NGOs, foundations, media, with opportunities for interactions all day and many evenings?
Hence, here we present a real quick overview for the busy policy maker with a focus on the all-important concept of ONE HEALTH, as the pillar of the Environment has been short-changed, as if an afterthought. To this day products and stewardship of antibiotic consumption gets the lion's share of funding, projects and attention.

In this book, seven broad Sections:

- The crucial role of WASH: Water-Soil-Sanitation-Wastewaters in dealing with COVID-19 as well as its role in the emergence, spread and control of AMR, with the Wellcome Trust, the Pasteur Institute and the Hong Kong University leadership in hosting EDAR 2019.

- Very thorough overviews of two related and much neglected issues: Aquaculture, with a top world expert from Japan, and Fungal AMR with an Australian leader in this domain.

- A big section on Infection Prevention and Control, with WHO-EMRO calling for a "culture of IPC", a message we would like to echo globally.

- And original lengthy architectural building expert view "Building Resilience to Face Pandemic (and extreme weather events), and the link with AMR airborne, with an original analysis of ARGs presence in hospital AC. A view on IPC and Patient Safety and a glimpse on overuse of catheters from a hospital case in the UAE, relevant to better practices to allow for improved IPC & AMR work.

We are conceptualizing the theme: ***"Building a culture of IPC in a One Health AMR"***

- We report on the first World Summit on Global Health Security attended in Australia in 2019, and which – with the John Hopkins GHS Index – motivated our book title. And we open the debate on economic response, at an important time with a new US Administration planning on infrastructural investments. If we take a broad, rapid view of LMIC, massive WASH investments, not austerity - not debt repayment in Africa - would face COVID19, as well as AMR, avoiding deaths and disabilities.

- Lastly: among the NCDs, it is cancer which has the closest link to AMR, hence the STELLA initiative with Oxford University and CERN; and in these times of increased mobilization on women, we have chosen an LMIC field African project for/with women in pregnancy: "Mambo Jama", as a glimpse of community approaches to safer care.

THE ENVIRONMENT FROM SURVEILLANCE TO SOLUTIONS

WASTEWATERS : KEY TO COVID-19 & AMR

SECTION I

THE ENVIRONMENTAL DIMENSIONS OF AMR IN REVIEW: WHERE HAVE WE BEEN AND WHAT MORE IS NEEDED?

> *Over the last few years there has been growing concern and mounting evidence that the environment plays a key, if not yet fully articulated, role in the selection and spread of antibiotic-resistant microbes. While progress has been made, consideration given to environmental dimensions in global and national approaches to AMR has not kept sufficient pace, undermining our collective response to AMR and commitment to One Health. Previous arguments for raising this sector up have not succeeded. We urgently need a step change in the way the environment is viewed and approached within the AMR agenda. Civil society and academia have previously led the way, but we now need policy and practice communities to take greater ownership and act decisively on this issue.*

Sian WILLIAMS, Policy Adviser, Drug-Resistant Infections, Wellcome Trust
Timothy JINKS, Head of Drug-Resistant Infections, Wellcome Trust

A WELLCOME PERSPECTIVE

In 2018, Wellcome co-hosted the 'International Environmental AMR Forum' in partnership with the US Centers for Disease Control and the UK Foreign Office's Science and Innovation Network. Reporting from this meeting and associated working groups aimed to lay out a comprehensive view of the existing knowledge base, outstanding questions and importantly areas readily available for policy action[1].
This meeting made clear to us that hot spots for environmental contamination and spread are well defined and extensively investigated by an established research community. Further, there is clear evidence that AMR risks stemming from the environment are heightened by human-generated contamination of waterways, sewage, soils and crops with antimicrobials, antimicrobial resistance genes and pathogens. While data and knowledge gaps persisted, particularly around the scale of direct impact environmental sources of AMR present to human health, the message from the community was clear despite these gaps, there is sufficient evidence to know environmental contamination increases AMR risk to people, and that policymakers and other practitioners should take actions now to prevent avoidable harm. In the time since this meeting, Wellcome has explored opportunities to support and advocate for this sector. We recognise that to successfully reduce AMR through a One Health approach – as is laid out in the WHO Global Action Plan on AMR[2] – there is a need to more strongly and more quickly bring understanding about the impact of environmental dimensions of AMR into broader AMR discussions and the subsequent design and implementation of national action plans.
It is our strong belief that not doing so will not only undermine our response to AMR, but also global health security, particularly where many points of environmental contamination stem from human, animal or industrial waste streams and can be readily controlled. Despite strong voices from within the academic and civil society communities, this vulnerability remains, and the environmental sector continues to fall behind the human and animal sectors in terms of development and implementation of AMR-related policies and practices[3].

WHERE HAS PROGRESS BEEN MADE?

Of course, in the last two years we have seen progress, but results have been mixed[4]. Connectivity and interdisciplinarity within the research community has grown, collectively generating evidence that can make a more compelling case for the environment as a transmission pathway for resistance and a cross-cutting issue within the AMR agenda. Case studies show human resistant infections can stem from environmental sources[1], and new research is showing us that resistance can emerge in environmentally-relevant mixtures at lower antibiotic concentrations than previously thought[5].
Despite this, evidence pointing to the environment as a reservoir for emergence of resistance is still often brushed off as circumstantial with limited concrete implications for human health risk, and research funding in the environment field remains relatively low[6].

At the same time, it can be said that consideration for the environment in policy-circles has risen, with stronger representation of this sector in some national action plans. However, this remains limited to high income countries and commitments remain largely focused upon data generation and research measures rather than clear policy change. This has left issues like treatment of hospital waste, farm run off and community sewage particularly neglected as remit for clinical practices and water standards largely sit with national governments. There are exceptions to this rule; for example, in their revised AMR action plan launched in 2020, Sweden has committed to upgrading wastewater treatment technology to target pharmaceutical residues[7].

Initiatives to curb antibiotic manufacturing pollution have taken for more promising steps. While a great deal of initial activity has been based on voluntary work from the pharmaceutical sector to clean up practices – particularly the AMR Industry Alliance, a body of 100 life sciences companies and associations who have launched their own framework for manufacturing standards to mitigate AMR[8] – calls for more formal regulation have been growing. A handful of countries, including Sweden and Norway, have piloted inclusion of environmental criteria in medicine procurement exercises, with indication that wider interest in this kind of approach is growing[9]. Most significantly, in early 2020 the Indian Ministry of Environment, Forest and Climate Change launched the draft notification 'Environment Protection Amendment Rules 2020'[10]. This proposal marked plans for the first national standards on antimicrobial levels in pharmaceutical manufacturing effluent. This is a potentially major step given the substantial proportion of the global antibiotic manufacturing industry based in India. Of course, implementation of a policy of this kind would require a delicate balance to ensure changes in the sector do not bar antibiotic manufacturing from being a viable business, avoiding unintended consequences on manufacture and supply of key medicines. However, the approach to this policy remains too unclear as the draft notification has met with significant opposition – notably from the Indian Drug Manufacturers Association – and is yet to be ratified. Abandonment of this significant proposed policy change, the most ambitious to date on this topic by any G20 government, would be a huge blow to the great progress already being made in this sector.

On a global level, the environmental representation we had hoped to see more strongly incorporated in the tripartite has not materialised. Recommendations from the UN Inter-Agency Coordination Group (IACG) for AMR suggested greater integration of the UN Environment Programme into tripartite activity was needed to support Member States in addressing AMR within environmental policy making[11]. However, the involvement of this group has been limited and thus so is the mandate for working on the environmental theme at the highest levels.

WHAT NEXT FOR ENVIRONMENT AND AMR?

Movement across the environmental dimensions of AMR is encouraging, but something further is needed to create the step change necessary to bring this issue up more strongly alongside human and animal sectors. Only then can we be assured of a comprehensive response to AMR and global health security through a true One Health approach. The argument that lack of understanding of risk is not the same as lack of risk and that a precautionary approach is appropriate has not landed. The fundamental limitation we face is not lack-of-evidence, cost or access to technology, but the way environment is viewed and prioritised by key actors across policy and practice communities in both the public and private sectors. A change in approach is urgently needed to encourage these groups to support this issue and take action. Any change must start with strengthening how evidence is communicated to decisionmakers. We have evidence and so we must think further on how this can be translated into arguments that better engage and encourage key actors where they are. Systematically bringing together existing studies to help stakeholders interpret data could provide significant support, tailoring readouts based on different stakeholder types to point to clear and relevant actions; noting that "removal of resistance genes" is not a tangible action for the majority of policy-makers. Alternative communication approaches and frames should also be explored, especially those that might make a stronger case for environmental issues in low and middle-income countries; for example, considering this as a pollution issue may help generate additional support from previously untapped sources.

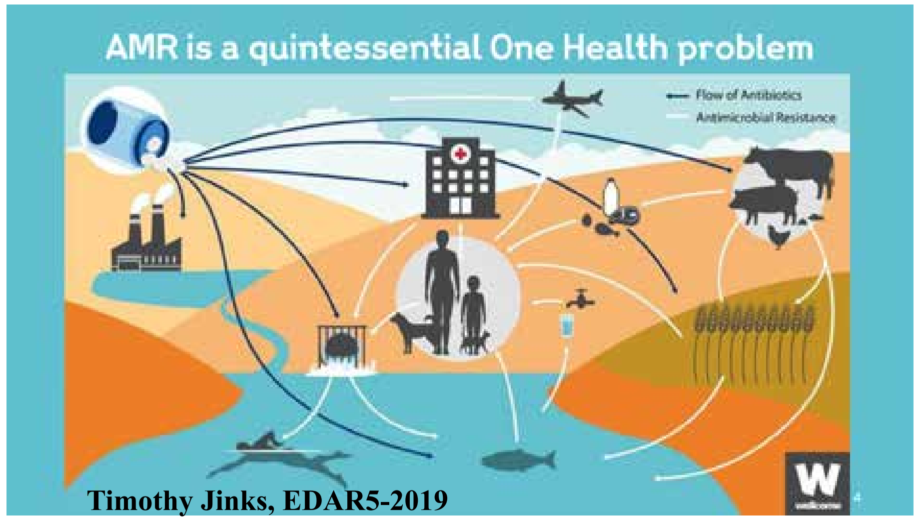
Any shift changes in how we translate evidence for action must also have a stronger shared understanding of risk at the heart. Communication of risk has been an ongoing challenge for the environmental theme, especially as relates to the direct impacts environmental dimensions of AMR pose to human health. Quantification of this risk is frequently cited as a requirement before any action can be taken.

We must be clearer that tracing back complex evolutionary pathways to fully identify the scope and scale at which environmental sources of AMR lead to human drug-resistant infections is not feasible.
Having these discussions with stakeholders might encourage clearer shared expectations of evidence in this field, and place greater value on the available circumstantial evidence. Further, engagement with policy and practice actors could be used to better define the type of evidence that best informs the taking of proportionate action. For example, quantification of the risk of inaction might make a stronger case for acting under precaution, or economic studies to weigh up required investment for an intervention against benefits that it will bring in terms of health and wellbeing, AMR related or otherwise. We might then use this understanding of the evidence-decision making nexus to tailor scientific approaches accordingly – after all, if evidence should be used to inform policy, we should also think about how policy needs can inform the research questions we are asking This might highlight, for example, the need to make stronger use of transdisciplinary measures, social sciences or focus on human health, if this is the key to unlocking prioritisation of environmental issues at the highest levels.

ENVIRONMENT WITHIN THE AMR SYSTEM

When it comes to the environment there may also be a compelling case to be made with regard to the many interfaces this sector has with wider AMR issues across human, animal and crop health. Consideration of environment through a systems lens may provide an interesting proposition, demonstrating how relevant interventions could be used as a lever to realise benefits across AMR and public health more widely, but also how the environment can end up as a sink for bad practices and suffer as a result of unintended consequences.

For example, we are well aware of the potential of wastewater to act as an early warning system in the cases of Polio and even COVID-19, so environmental dimensions have significant scope to be strongly brought into AMR surveillance and mitigation efforts in a more holistic way. Similarly, it should be recognised that the most promising actions in the environmental sector are largely AMR-sensitive rather than specific, and have scope to have co-benefits for broader development, public health and environmental health priorities, including many targets across the Sustainable Development Goals. While we should all consider individual actions that might better support the case for action across environmental dimensions of AMR, success will require collective efforts and engagements between academic, civil society, policy and practice communities. Academia and civil society have provided strong voices thus far, but we must now hand over the torch and call on policy and practice communities to take greater ownership and act decisively on this issue. We should take heart from the progress made, learn from missed opportunities, and strive to make the next steps even stronger.



Timothy Jinks, EDAR5-2019

Sian WILLIAMS is Policy Adviser for Wellcome Trust's Drug Resistant Infections Priority Programme. Her main interest lies in translating science for evidence-based policy, leading work focused on environmental dimensions of AMR and behaviour change for antimicrobial stewardship. Sian studied Natural Sciences at the University of Cambridge and holds a Masters in Science Communication from Imperial College London. Prior to joining Wellcome, Sian worked for the UK Government's Global Food Security programme.

Dr Timothy JINKS is the Head of Wellcome's Drug-resistant Infections priority program leading Wellcome's efforts directed at reducing the threat of AMR. In his preceding role he led the development of Wellcome's strategic plan to address drug-resistant infections. He is a member of the CARB-X Joint Oversight Committee, the Longitude Prize Committee and is non-executive Director of ReViral Ltd.

References

(1) Centers for Disease Control and Prevention, UK Science and Innovation Network, Wellcome Trust. Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges. 2018.
https://wellcome.ac.uk/sites/default/files/antimicrobial-resistance-environment-report.pdf

(2) World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015.
https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1

(3) World Health Organization. Monitoring global progress on addressing antimicrobial resistance: Analysis report of the second round of results of AMR country self-assessment survey 2018.
https://apps.who.int/iris/bitstream/handle/10665/273128/9789241514422-eng.pdf?ua=1

(4) AMR landscaping study commissioned by the Wellcome Trust, publication in preparation.

(5) Stanton, I.C., Murray, A.K., Zhang, L. et al. Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration. Commun Biol 3, 467 (2020).
https://doi.org/10.1038/s42003-020-01176-w

(6) JPIAMR. Mapping of AMR Research Funding. 2019.
https://www.jpiamr.eu/wp-content/uploads/2019/02/Mapping-of-AMR-research-funding-2017-report.pdf

(7) Government Offices of Sweden. Swedish Strategy to Combat Antibiotic Resistance, 2020-2023.
https://www.government.se/499178/globalassets/government/dokument/socialdepartementet/amr_strategi_eng_web.pdf

(8) AMR Industry Alliance. Common Antibiotic Manufacturing Framework. 2018.
https://www.amrindustryalliance.org/wp-content/uploads/2018/02/AMR_Industry_Alliance_Manufacturing_Framework.pdf

(9) Tiley, A. Perspective on Pharma: Tackling AMR through sustainable antibiotic production. European Pharmaceutical Manufacturer. 2019. https://www.epmmagazine.com/opinion/tackling-amr-through-sustainable-antibiotic-production/

(10) The Government of India. Ministry of Environment, Forest and Climate Change Notification. 2020.
https://www.documentcloud.org/documents/6770398-The-following-draft-of-the-notification-which.html

(11) Interagency Coordination Group on Antimicrobial Resistance. No Time To Wait: Securing The Future From Drug-Resistant Infections. 2019.
https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

WASTEWATER-BASED EARLY WARNING SYSTEMS FOR COVID-19

Abstract

Wastewater-based epidemiology is almost 20 years old. First applied to the assessment of drug use, this approach has the advantage of not being intrusive, of being anonymous, and of being able to be carried out continuously. It is also inexpensive. This wastewater-based epidemiology made it possible to determine locally or regionally which narcotics were used the most and the weekly variations in their consumption or even the qualitative and quantitative changes over several years of their use.

Very quickly this approach was applied to monitoring antibiotic resistance by detecting resistant bacteria and also their resistance genes. In the same type of process, many enteric viruses such as enteroviruses, rotaviruses or noroviruses, all naked viruses, were also found in wastewaters and monitored through their analysis. Based on protocols developed within the framework of the World Health Organization's polio eradication program, these viruses could be concentrated and detected, even going as far as sequencing their genomes. These concentration and detection protocols had to be adapted for enveloped viruses such as coronaviruses. As SARS-CoV-2 is found in the faeces of infected people, and as the percentage of presymptomatic or asymptomatic people is high, several teams around the world thought about and succeeded in detecting this new virus in untreated wastewaters, and this, as for other viruses mentioned above, several days or even weeks before the appearance of clusters of human clinical cases among the population concerned by the wastewater treatment plants studied.

“*Wastewater-based epidemiology is almost 20 years old...*
This approach was applied to monitoring antibiotic resistance by detecting resistant bacteria and also their resistance genes.
As SARS-CoV-2 is found in the faeces of infected people, several teams around the world thought about and succeeded in detecting it in untreated wastewaters several days or even weeks before the appearance of clusters of human clinical cases.”

Jean-Claude MANUGUERRA, Institut Pasteur, head of "Environment & Infectious Risks", Lab for Urgent Response to Biological Threats, (Cellule d'Intervention Biologique d'Urgence) CIBU, Paris, France
Christophe BATÉJAT, Deputy Head of CIBU, Institut Pasteur, Paris, France
India LECLERQ, University of Paris, Cellule Pasteur, & CIBU, Institut Pasteur, Paris, France
Thomas LABADIE, University of Montpellier, CNRS (National Center for Scientific Research) UMR 5048, Center for Structural Biochemistry (CBS), Montpellier, France

Almost 20 years ago, the idea of linking environmental sciences and social sciences in the field of drug use was born. The aim was to resort to a non-intrusive approach to monitor the use of these products by analysing untreated wastewaters in treatment plants (Daughton, 2001). Anonymous, collective and population based, this surveillance has made it possible, and still allows us, to know the drugs consumed, their relative importance and the trends in their use. Until then, the monitoring of drug consumption was assessed through medical or criminal statistical data or by sociological surveys, and this on an intermittent basis. The active molecules of narcotics, or their metabolites, are excreted in the urine and faeces which are collected via the sewer system and are found in particular at wastewater treatment plants. These molecules are stable enough to be detected long enough (from a few hours for cocaine to a few days for methamphetamine at room temperature) after they are excreted. This idea of Daughton was applied as early as 2005 to monitor cocaine consumption in Italy in the Po plain through the analysis of collected wastewaters by mass spectrometric detection of cocaine and its main metabolite, benzoylecgonine.

Zuccato and colleagues were thus able to determine that the average daily consumption was 27 +/- 5 doses of cocaine per 1000 adults, which according to these authors was much higher than the official estimates then available (Zuccato et al., 2005). Since the mid-2010s, the notion of wastewater based epidemiology has emerged. Improvements in efficient, more quantitative and inexpensive analytical techniques, have made it possible to refine data on the use of drugs such as cocaine.

For example, DNA-directed immobilisation of aptamer sensors, have detected cocaine concentrations as low as 10 nm. By monitoring cocaine concentrations by this method for 7 consecutive days, Yang et al. showed that consumption is higher during weekends than during weekdays (Yang et al., 2016), demonstrating a trend already shown using tandem analysis by liquid chromatography and mass spectroscopy in Germany (Ort et al., 2014).

By monitoring substances in the water of a sewage treatment plant near Barcelona in Spain for 5 years, Mastroiani and collaborators were able to determine that alcohol, cannabis and cocaine were the products most consumed by the population covered by the study, with an increasing trend during the study period and that consumption was higher during the weekend for alcohol, cocaine and methylene-dioxymethamphetamine (MDMA) (Mastroianni et al., 2017).

Recently, such a study in Europe showed regional differences on the continent: cocaine (in fact its main metabolite) was in highest quantity in Western and Southern Europe while in Eastern and in Northern Central Europe it was amphetamine, MDMA and methamphetamine, that were found in greater quantities (González-Mariño et al., 2020). Other chemical molecules can also be found in wastewater treatment plants. The massive use of antibiotics both in human and animal health as well as in agriculture has led to their accumulation in the environment and the selection of antibiotic resistant bacteria (AMR bacteria) and their antibiotic resistance genes (AMR genes).

While studies on AMRs first focused on the clinical and epidemiological contexts of their development, subsequent studies have shown that the emergence of such resistance in the environment, in particular in sewage, also plays a very important role. Thus, many articles report the results of studies of AMR monitoring in wastewaters from treatment plants. They were able to identify major trends such as the spread and increase in resistance to fluoroquinolones across the European continent between 2002 and 2012 (Hughes, 2014). Other articles in this dossier “AMR & the Environment, a GHS issue”, talk about it.

Viruses that are secreted from the intestinal tract of infected humans, such as noroviruses, rotaviruses, polioviruses, Hepatitis A and E viruses are also commonly detected in wastewaters. Viruses secreted from infected animals can also be found in lakes or rivers, like influenza viruses secreted by infected waterfowls. Once in water, viruses remain infectious for a certain period until complete inactivation. The detection of inactivated virus in water remains possible, using DNA amplification technologies such as PCR (polymerase chain reaction) that reveals the presence of persistent viral genes, protected by the virus capsid.

Generally, enveloped viruses that are wrapped in a lipid membrane (such as the SARS-CoV-2) tend to persist less in the environment than naked viruses. Beside the virus structure, the main parameters driving virus persistence in water are the temperature, pH and salinity as well as the presence of ultraviolet radiations from solar light, for review (Pinon & Vialette, 2018). Of interest, it has also been observed that the presence of sludge has a protective effect on virus persistence in water. Experimental observations on influenza viruses, demonstrated that virus particles could remain infectious up to 12 days in water at 37°C and more than two years at 4°C (Dublineau et al., 2011). In some cases, interhuman transmission of these waterborne viruses can occur, particularly with highly persistent viruses such as noroviruses, for review (Pinon & Vialette, 2018). In some cases, interhuman transmission of these waterborne viruses can occur, particularly with highly persistent viruses such as noroviruses, for review (Pinon & Vialette, 2018). As part of the WHO poliovirus eradication program, surveillance for acute flaccid paralysis has been supplemented by testing for polio viruses in sewage treatment plants in many countries. Moreover, the methods used for other enteric viruses are those initially developed and applied for polioviruses. The viruses that have been monitored in wastewater from sewage treatment plants are: noroviruses, enteroviruses, Aichi viruses, parechoviruses, hepatitis A and E viruses, astroviruses, rotaviruses and adenoviruses. All these viruses are naked viruses. This surveillance detected the viruses several days before the first symptomatic cases in humans requiring medical consultation.

For example for noroviruses, a study in Sweden based on collecting samples of untreated wastewaters every two weeks between January and May 2013, showed that the greatest amount of noroviruses was detected in these wastewaters 2 to 3 weeks before most patients were diagnosed with this infection in Gothenburg (Hellmér et al., 2014). So this is an approach on which to base an early warning system.

This type of surveillance can also reveal a silent viral circulation, that is to say without symptomatic cases or very few, as has been done in France where the silent circulation of enterovirus D68, and hepatitis A and E viruses has recently been demonstrated (Bisseux et al., 2018). In addition, this study indicated that the sequences of the viruses found in wastewaters are comparable to those obtained from the viruses in the very small number of patients, establishing a direct link between the two.

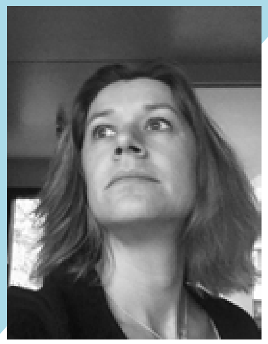
Most protocols include concentration steps of wastewaters in order to concentrate virus particles. They have originally been applied to naked viruses and need to be significantly adapted for enveloped viruses such as coronaviruses. It has been shown that SARS-CoV-2, the causative agent of COVID-19, can be found in the faeces of patients with the disease, even after it has disappeared from their respiratory system.

It has also been shown that traces of this coronavirus have been found in wastewaters from treatment plants (for review (Foladori et al., 2020)). SARS-CoV-2 genome can be detected up to 25 days in wastewater at 37 ° C, and much longer at 4 ° C. Furthermore, it is now recognized that a variable but not insignificant proportion, on average 40 to 45%, of infected persons are presymptomatic or remain asymptomatic (Madewell et al., 2020).

Considering these 2 types of data and the experience gained with other viruses, a number of studies have looked for SARS-CoV-2 in wastewaters from sewage treatment plants. Thus Ahmed et al. were among the first to do so (Ahmed et al., 2020). They demonstrated the presence of SARS-CoV-2 genome in untreated waters from a wastewater treatment plant in Australia twice in 6 days. Using a model fed by the demographic data of the basin drained by this station and the quantities of viral genome found in untreated water, the authors estimated the presence of 171 to 1,090 infected people in this catchment population. In France, a study of wastewater collected in the main wastewater treatment plant of Montpellier 4 days before exiting lockdown and 70 days after, revealed the presence of SARS-CoV-2 genome from mid-June 2020, while the incidence of new cases did not start to increase until 2 weeks later (Trottier et al., 2020). It is noteworthy that, until now, no SARS-CoV-2 contamination from wastewaters has been reported. In the United States, the Centers for Disease Control and Prevention and the US Department of Health and Human Services, with the collaboration of other federal agencies in the country, have set up the National Wastewater Surveillance System for COVID-19. The aim is to supplement the surveillance of clinical cases confirmed by laboratory tests which are either too little used or not available (CDC, 2020). Thus, the environmental approach to COVID-19 surveillance makes it possible to establish an early warning system and to monitor outbreaks of SARS-CoV-2 infection, in real time at a low cost.

Dr. Jean-Claude MANUGUERRA is the head of the Expertise and research Unit "Environment and infectious risks", of the Laboratory for Urgent Response to Biological Threats, (CIBU) and of the OIE collaborating Centre for the Detection and Identification in Humans of Emerging Animal Pathogens and Development of Tools for their Diagnoses, and Deputy Director of the French National Reference Centre for Hantaviruses at the Institut Pasteur, Paris.
He was originally qualified as a veterinarian and was trained in virology at Institut Pasteur in order to get his PhD. He spent two years as a post doctoral fellow at the National Institute for Medical Research (London, United Kingdom). He was then co-director of the National Influenza Centre for Northern France and of the WHO Collaborative Centre for Research and Reference on Influenza Viruses and Other Respiratory Viruses, one of the 13 laboratories included in the WHO Collaborative Multi-Centre Laboratory Network on SARS (1994-2003). He belonged to the French team sent to Hanoi for the control of the SARS outbreak at the Hanoi French Hospital in March 2003. Since then, he participated to a number of missions during outbreaks. In 2014 and 2015, he went to the Ebola diagnostic laboratory in Donka Hospital in Conakry and in the Ebola Treatment Center in Macenta in Guinea respectively. Since 2014 he is the workpackage leader of the human virology network of the MediLabSecure project. From 2000 to 2018, he was a member of the Steering Committee of the Global Alert and Response Network coordinated by the WHO and chaired it from 2011 to 2013.

Mr Christophe BATEJAT, MsC, Deputy Head of the Laboratory for Urgent Response to Biological Threats. Christophe Batejat is an engineer in virology and biosafety. He is the deputy-head of the Laboratory for Urgent Response to Biological Threats (CIBU)/ Unit “Environment and Infectious Risks” (ERI) at Institut Pasteur in Paris. His research focuses on viruses survival outside their hosts and he was involved in emergency diagnosis and characterization of the COVID-19.



Prof. India LECLERCQ, PhD, HDR India Leclercq is assistant Professor at Université de Paris, doing her research in the ‘Environment and Infectious risks’ Unit at Institut Pasteur in Paris, on the persistence of influenza virus in the environment.

Dr Thomas LABADIE, PhD, Postdoctoral researcher
Thomas Labadie is a postdoctoral researcher specialised in virology, his past researches focused on the persistence of influenza virus in the environment (Institut Pasteur, Paris) and the cellular biology of the bluetongue virus (London School of Hygiene and Tropical Medicine, London). He is currently studying the evolution of insect densoviruses, using synthetic biology and high-throughput mutagenesis methods (Centre for Structural Biology, Montpellier).

References

Ahmed, W., Angel, N., Edson, J., Bibby, K., Bivins, A., O'Brien, J. W., Choi, P. M., Kitajima, M., Simpson, S. L., Li, J., Tscharke, B., Verhagen, R., Smith, W. J. M., Zaugg, J., Dierens, L., Hugenholtz, P., Thomas, K. V., & Mueller, J. F. (2020). First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: A proof of concept for the wastewater surveillance of COVID-19 in the community. Science of The Total Environment, 728, 138764.

Bisseux, M., Colombet, J., Mirand, A., Roque-Afonso, A.-M., Abravanel, F., Izopet, J., Archimbaud, C., Peigue-Lafeuille, H., Debroas, D., Bailly, J.-L., & Henquell, C. (2018). Monitoring human enteric viruses in wastewater and relevance to infections encountered in the clinical setting: A one-year experiment in central France, 2014 to 2015. Eurosurveillance, 23(7). https://doi.org/10.2807/1560-7917.ES.2018.23.7.17-00237

CDC. (2020, octobre 23). National Wastewater Surveillance System. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/wastewater-surveillance.html

Daughton, C. G. (2001). Illicit Drugs in Municipal Sewage. In Pharmaceuticals and Care Products in the Environment (Vol. 791, p. 348-364). American Chemical Society. https://doi.org/10.1021/bk-2001-0791.ch020

Dublineau, A., Batéjat, C., Pinon, A., Burguière, A. M., Leclercq, I., & Manuguerra, J.-C. (2011). Persistence of the 2009 Pandemic Influenza A (H1N1) Virus in Water and on Non-Porous Surface. PLOS ONE, 6(11), e28043. https://doi.org/10.1371/journal.pone.0028043

Foladori, P., Cutrupi, F., Segata, N., Manara, S., Pinto, F., Malpei, F., Bruni, L., & Rosa, G. L. (2020). SARS-CoV-2 from faeces to wastewater treatment: What do we know? A review. Science of the Total Environment, 13.

González-Mariño, I., Baz-Lomba, J. A., Alygizakis, N. A., Andrés-Costa, M. J., Bade, R., Bannwarth, A., Barron, L. P., Been, F., Benaglia, L., Berset, J.-D., Bijlsma, L., Bodík, I., Brenner, A., Brock, A. L., Burgard, D. A., Castrignanò, E., Celma, A., Christophoridis, C. E., Covaci, A., ... Ort, C. (2020). Spatio-temporal assessment of illicit drug use at large scale: Evidence from 7 years of international wastewater monitoring. Addiction (Abingdon, England), 115(1), 109-120. https://doi.org/10.1111/add.14767

Hellmér, M., Paxéus, N., Magnius, L., Enache, L., Arnholm, B., Johansson, A., Bergström, T., & Norder, H. (2014). Detection of pathogenic viruses in sewage provided early warnings of hepatitis A virus and norovirus outbreaks. Applied and Environmental Microbiology, 80(21), 6771-6781. https://doi.org/10.1128/AEM.01981-14

Hughes, D. (2014). Selection and evolution of resistance to antimicrobial drugs. IUBMB Life, 66(8), 521-529. https://doi.org/10.1002/iub.1278

Madewell, Z. J., Yang, Y., Longini, I. M., Halloran, M. E., & Dean, N. E. (2020). Household transmission of SARS-CoV-2: A systematic review and meta-analysis of secondary attack rate. MedRxiv: The Preprint Server for Health Sciences. https://doi.org/10.1101/2020.07.29.20164590

Mastroianni, N., López-García, E., Postigo, C., Barceló, D., & López de Alda, M. (2017). Five-year monitoring of 19 illicit and legal substances of abuse at the inlet of a wastewater treatment plant in Barcelona (NE Spain) and estimation of drug consumption patterns and trends. The Science of the Total Environment, 609, 916-926. https://doi.org/10.1016/j.scitotenv.2017.07.126

Ort, C., Eppler, J. M., Scheidegger, A., Rieckermann, J., Kinzig, M., & Sörgel, F. (2014). Challenges of surveying wastewater drug loads of small populations and generalizable aspects on optimizing monitoring design. Addiction (Abingdon, England), 109(3), 472-481. https://doi.org/10.1111/add.12405

Pinon, A., & Vialette, M. (2018). Survival of Viruses in Water. Intervirology, 61(5), 214-222. https://doi.org/10.1159/000484899

Trottier, J., Darques, R., Ait Mouheb, N., Partiot, E., Bakhache, W., Deffieu, M. S., & Gaudin, R. (2020). Post-lockdown detection of SARS-CoV-2 RNA in the wastewater of Montpellier, France. One Health (Amsterdam, Netherlands), 10, 100157. https://doi.org/10.1016/j.onehlt.2020.100157

Yang, Z., Castrignanò, E., Estrela, P., Frost, C. G., & Kasprzyk-Hordern, B. (2016). Community Sewage Sensors towards Evaluation of Drug Use Trends: Detection of Cocaine in Wastewater with DNA-Directed Immobilization Aptamer Sensors. Scientific Reports, 6, 21024. https://doi.org/10.1038/srep21024

Zuccato, E., Chiabrando, C., Castiglioni, S., Calamari, D., Bagnati, R., Schiarea, S., & Fanelli, R. (2005). Cocaine in surface waters: A new evidence-based tool to monitor community drug abuse. Environmental Health: A Global Access Science Source, 4, 14. https://doi.org/10.1186/1476-069X-4-14. https://doi.org/10.1016/j.scitotenv.2020.138764

WASTEWATER SURVEILLANCE TO FOCUS MORE ON HUMAN PATHOGENS

Interview, Professor Tong Zhang,
The University of Hong Kong

by Garance F. Upham

Professor Tong ZHANG Environmental Microbiome Engineering and Biotechnology Laboratory, Department of Civil Engineering, The University of Hong Kong, China.
Organizer and co-Chair EDAR5 2019 (with Dr K. Fukuda, formerly ADG, AMR, WHO)

Garance Upham: *Among the members of the newly created US President Biden COVID-19 group, we noted that Dr Michael Osterholm, Director of the CIDRAP (Center for Infectious Disease Research and Policy at Minnesota University) an expert group on AMR – is doing strong advocacy for wastewater surveillance, both as an excellent approach to COVID-19, as well as for AMR, which he sees as may be a better method than the GLASS model followed by many countries with the WHO up to now. My question to you: Speaking to policymakers who are not specialists in AMR, could you explain the benefits of wastewater surveillance for AMR?*

Prof. Tong Zhang: What's the benefits of wastewater testing? To me, I consider wastewater as a collective sample of, say, thousands of people. Hence, it is a very cost-effective approach to conduct surveillance and prevention for a large group of people. In Hong Kong, for example, one single plant may treat wastewater of large groups of people, 100 thousand people or more, so if you take that sewage, you have a representative sample and an excellent approach to surveillance.
That is why we should promote wastewater surveillance of AMR and actually not only for the special case of AMR; but also to focus on human pathogens surveillance in general, and viruses like COVID-19.

Question: *Are you doing COVID-19 surveillance in China, what are the advantages of doing so?*

Prof. Tong Zhang: Yes, we are doing it in Hong Kong, I am leading a project on that. In general, wastewater surveillance allows health authorities to see the rise in infection rates and anticipate outbreaks, since there is SARS-CoV2 excretion in faeces before people get sick or just get tested.

Question: *Can you tell us what you know in the USA, or other countries? I recall Senator Diane Feinstein has been campaigning for national COVID-19 wastewater surveillance.*

Prof. Tong Zhang: There are many local or national programs in countries around the world. To give but a few examples, there is a £1 million program, led by the Centre for Ecology & Hydrology in the United Kingdom, a $10 million state wide program in the State of Michigan in the USA, there is a research project by the US Wisconsin Department of Health Services, and in late September the American Health & Human Services was reported to want to test 30% of U.S. wastewater for the coronavirus as an 'early warning system'. Then Singapore is testing human poo for coronavirus. And of course Paris Water (Eau de Paris) has done some of that. Many localities and countries around the world have undertaken such surveillance, too numerous to be listed here. But now it would be good if it became standard international practice as a way to help us beat the pandemic. And the more the tools and funding for this surveillance is in place, the better equipped we may be for AMR surveillance.

Question: *What about LMIC, some of us campaigning for WASH. WHO Director General Dr Tedros talked of it on Nov 4?*

Prof. Tong Zhang: Water, Sanitation Hygiene, often talked of as "WASH" are very important. People have known the significance of clean water for several centuries. In China, back a thousand years ago, people knew to boil the water before drinking it, using it for cooking. Even for the average family, not just rich family, when they travelled, they figured out that they needed to boil the water each time they settled, first thing to do!
So I think the basic WASH is very important for the low and middle income countries (LMICs). Probably the most cost-effective intervention to stop diseases and combat pathogens which may be, or develop to become, antimicrobial resistant.

Question: *Would you have a listing of what technologies are best to use to prevent AMR being released in wastewater?*

Prof. Tong Zhang: I'm not an expert on membrane technology, but I know it could be applied worldwide widely everywhere, even in middle income country, to treat the wastewater. Since most resistance is carried by bacteria, if you can remove bacteria then you can reduce the potential for gene transfer.

Question: *What do you think are the weaknesses concerning wastewater surveillance on AMR as presently ongoing?*

Prof. Tong Zhang: We are using molecular techniques, but how can it be connected to phenotype of resistance from clinical data is weak. We need a lot more work on that. Most work on wastewater is focusing on the microbiome, in it there could be many environment bacteria which may not be human pathogens, yet we should focus on the latter, to have a better surveillance mechanism for all pathogens, whether drug-resistant or not.

Addendum:
COVID-19 Surveillance in Hong Kong.

Our work on sewage test is also helping Hong Kong to face COVID-19, now, especially in recent days, We tested 300 samples in the 4th wave of COVID-19 at Hong Kong. The results correlated very well with the outbreaks in the community. Recently, the method has been used for tests of individual buildings. Government issued the mandatory test order based on our results for one building on Dec. 28, while there was no case in that building, at least four positive cases so far had been found from the mandatory tests of ~2000 residents.

On Dec. 30, HK Government issued another mandatory test order to another building based on our sewage test results when there was no case reported in that building. Up to now, at least one positive case has being found in this second building.

So far, HK Government only issued these two mandatory test orders based on our suggestions and both of them helped picking out positives cases before clinical tests.

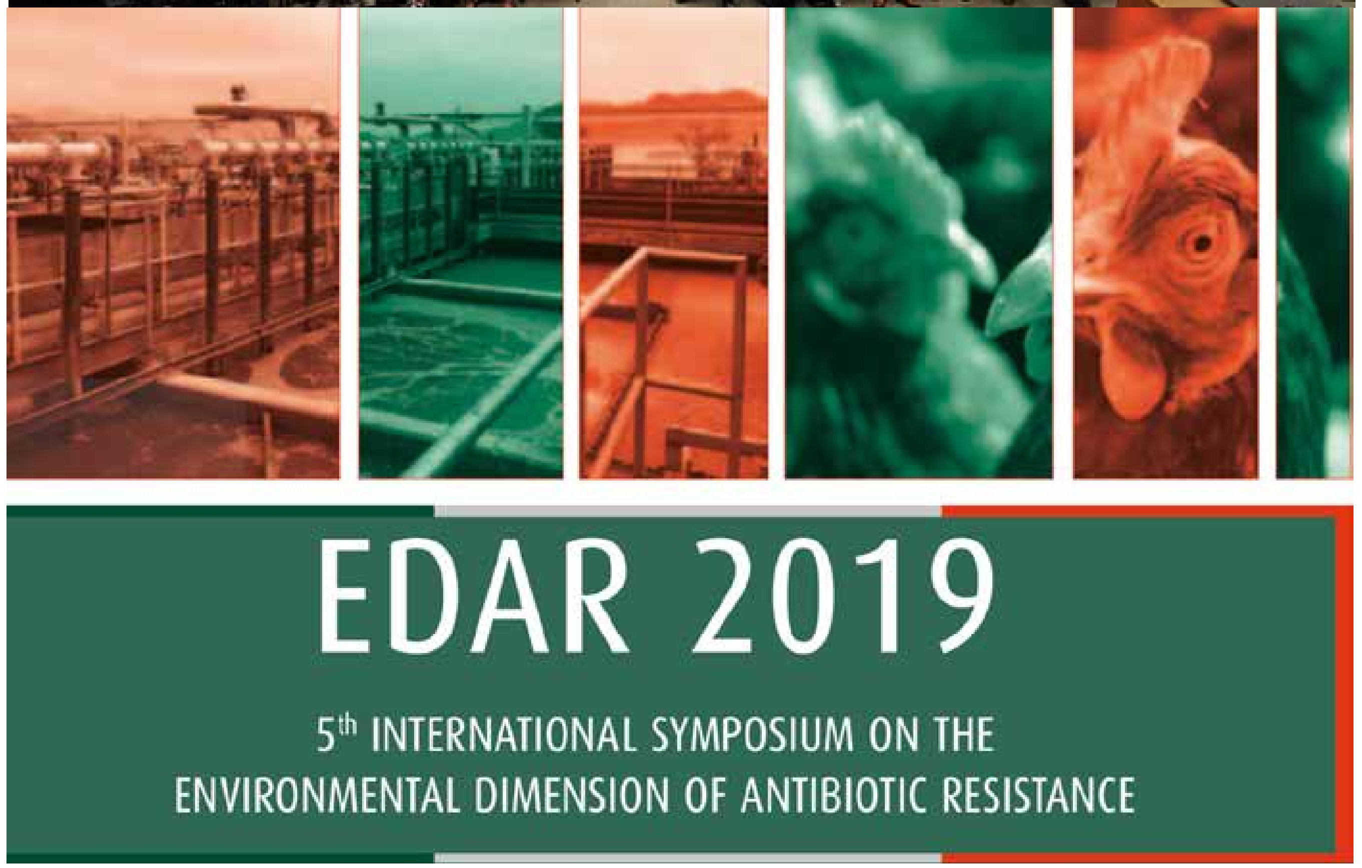
Here are links about this project and the relevant news.
https://www.hku.hk/press/news_detail_22201.html
https://www.scmp.com/news/hong-kong/health-environment/article/3115515/hong-kong-fourth-wave-covid-19-sewage-samples

Examples of press coverage:
- www.cranfield.ac.uk/press/news-2020/work-begins-on-uk-system-to-detect-covid-19-in-wastewater
- £1 million programme, led by the UK Centre for Ecology & Hydrology (UKCEH),
- https://www.michiganradio.org/post/state-puts-10-million-surveillance-network-covid-19-wastewater US$ 10 million
- https://www.jsonline.com/story/news/2020/06/18/researchers-attack-covid-19-new-way-tracking-virus-sewage/3191077001/ US$ 1.25 million
- https://www.cnbc.com/2020/09/25/hhs-wants-to-test-30percent-of-us-wastewater-for-the-coronavirus.html 2020/09/25 Department of Health and Human Services
- https://www.scmp.com/week-asia/health-environment/article/3088466/singapore-checking-peoples-poo-coronavirus

"These discussions between health, water and finance ministers are among the most important meetings of the year. Investing in water, sanitation and hygiene is critical to preventing both pandemics and local outbreaks. Its absence leaves us exposed"
Dr Tedros, on World WASH day, Nov. 4, 2020

EDAR 2019 at the University of Hong Kong
Group photo and cover of Abstracts Book.
And next page: Dr Li and Dr Zhang's scientific research article:

"TACKLING ENVIRONMENTAL´DIMENSION OF ANTIBIOTIC RESISTANCE GENES BY COMPREHENSIVE ASSESSMENT AND SOURCE CONTROL"



For the EDAR 2019 Book of Abstracts (pdf), write to: info@amrthinkdotank.org.

Next EDAR meeting should take place in Sweden, under Professor Larsson.

TACKLING ENVIRONMENTAL DIMENSION OF ANTIBIOTIC RESISTANCE GENES BY COMPREHENSIVE ASSESSMENT AND SOURCE CONTROL

Abstract

Antibiotic resistance is creating a crisis in public health, and it has been regarded as a challenge for humanity today. With its large number and diversity of bacteria and their complex interactions, the environment alone has been recognized as the single largest reservoir of antibiotic resistance genes (ARGs). However, strategies to control ARGs pollution in the environment are still in infancy as the environmental ARG profile remains poorly understood. Given regional differences in antibiotic resistance genes background and environmental management, it is necessary to perform systematic regional surveillance across local environments.

The comprehensive local mapping of antibiotic resistance genes will assist in tracking sources of ARG pollution in the environment and establish a risk assessment framework. This will largely facilitate identifying strategies that should be prioritized to tackle ARGs at critical control points in local environments. In the long-term, this will substantially ease health and environmental burden, contributing to sustainable development regionally and globally.

> ***"The critical role of the environment in the dissemination of antibiotic resistant genes has become more and more obvious. ...the wastewater treatment plant is an ideal environment where enteric and environmental bacteria mixed intensively. However, big knowledge gaps exist regarding the environmental dimension of antibiotic resistance, ranging from fundamental research questions such as transmission across human/animal and environmental interfaces to local effective control strategies."***

Dr Liguan LI, Environmental Microbiome Engineering and Biotechnology Laboratory, Department of Civil Engineering, The University of Hong Kong, SAR, China.

Professor Tong ZHANG, Environmental Microbiome Engineering and Biotechnology Laboratory, Department of Civil Engineering, The University of Hong Kong, Hong Kong, SAR, China.

Antibiotic resistance has become a global health crisis, threatening effective treatment of common infections caused by bacteria[1]. It will become worse if we do not act immediately to combat its current epidemic propagation worldwide. Mitigation of antibiotic resistance thus has become an urgent health challenge for human security, yet only limited progress has been made, as the environmental dimension has received less attention in the tripartite "One Health" approach: Human Health, Animal Health and The Environment. Indeed, research on antibiotic resistance has now been extended beyond clinical settings to include relevant environment especially those substantially impacted by human activities like agriculture and sewage system. In the past decades, the rapid development of high-throughput sequencing has largely been central to studies on environmental resistome (i.e., the collection of antibiotic resistance genes in a given environment). Studies have revealed the critical role of the environment in the dissemination of these genes. For example, soil microbiome, the long recognized evolutionary origin of antibiotic resistance, has been proved to be a reservoir of ARGs available for exchange with human pathogens[2]. In particular, multidrug-resistant bacteria retrieved from soil contain ARGs against clinically important antibiotic classes (like beta-lactams, aminoglycosides and tetracyclines), that match with ARGs retrieved from various human pathogens. A recognized hotspot of ARG occurrence is the wastewater treatment plant as it is an ideal environment where enteric and environmental bacteria mixed intensively. ARGs originated from human pathogens have been frequently detected in the activated sludge as revealed in our recent nine-year longitudinal study[3], which highlights that wastewater treatment plants are reservoirs of ARGs. The critical role of the environment in ARG dissemination has, therefore, become more and more obvious.

More importantly, as it is well-recognized that the health of humans is closely linked to the health of animals and the environment, a 'One Health' approach has been favored for antibiotic resistance containment strategies by national and international agencies, including, explicitly, the environment[4,5]. However, big knowledge gaps exist regarding the environmental dimension of antibiotic resistance, ranging from fundamental research questions such as transmission across human/animal and environmental interfaces to local effective control strategies.

SYSTEMATIC SURVEILLANCE OF ARG PROFILE ACROSS LOCAL ENVIRONMENTS

Combating antibiotic resistance in the environment first requires a comprehensive understanding of environmental resistome. Despite the insightful information on antibiotic resistance by clinical surveillance efforts, there is a dearth of data from systematic studies of antibiotic resistance in the environment. The metagenomic approach as a tool for ARG surveillance in various environments, has been proposed as a valuable option in a recent article in Science[6]. One notable example is to apply metagenomics based surveillance to human sewage for community surveillance of antibiotic resistance, since it can generate pooled data for a large population, as well as across ARGs and bacteria.

Such surveillance of sewage from 60 countries have revealed significant differences in abundance and diversity of ARGs among regions of Europe, North-America, Oceania, Africa, Asia, and South-America, strongly correlated with socioeconomic, health and environmental factors[7]. The first trans-Europe ARG surveillance of sewage also revealed that antibiotic use and environmental conditions were important factors related with resistance persistence and spread in European countries[8].

More worrisome, our recent findings on ARGs in drinking water distribution systems have raised concern for public health, as the human beings have direct contact with these systems in daily life[9]. Among the samples collected from 25 cities in China, South Africa, Singapore and the USA, obvious regional variations in ARG load in drinking water systems exist. Compared with China, a moderate ARG level was observed in samples from Singapore and the USA. Even in China alone, there are obvious region-specific ARG profiles.

These results highlight the need to implement local surveillance and control measures, based on specific conditions in different geographic regions. It also highlights the need for local coordinated efforts by multiple sectors to track and control the spread of antibiotic resistance, given the unique socioeconomic and geographical structure of each region. These efforts will especially benefit underdeveloped countries. For example, researchers characterized the ARG profiles of interlinked samples in two low-income Latin American communities in El Salvador and Peru, including hundreds of human faeces and environmental samples[10]. According to the unique local socioeconomic situation, they then specifically assessed the effectiveness of the people's excreta management strategies in reducing faecal bacteria and resistance genes in these settings.

Another similar case is in a Cambodian community[11], where faecal carriage of *Escherichia coli* and *Klebsiella pneumoniae* harbouring extended spectrum cephalosporinase genes are common. Through systematic surveillance, researcher identified women and young children as high risk groups, because in their specific community culture, they have more exposure to animal manure and slaughter products than others.

SOURCE TRACKING OF ARG POLLUTION IN THE ENVIRONMENT

The complex ARG profile, revealed by the large-scale surveillance, raises questions of public concern – where are the sources of ARG pollution and how to identify them?

Tracking antibiotic resistance in local environments is essential for source control. However, identifying transmission pathways of ARG pollution can be confounded by point and diffusion sources, as well as cross reactivity under complicated environmental conditions (Figure 1). The distinct fate and behaviour of ARGs in different environments further complicate the problem. Nevertheless, ever since the discovery of frequent ARG occurrences in human-related environments, identifying potential sources has received considerable attention.

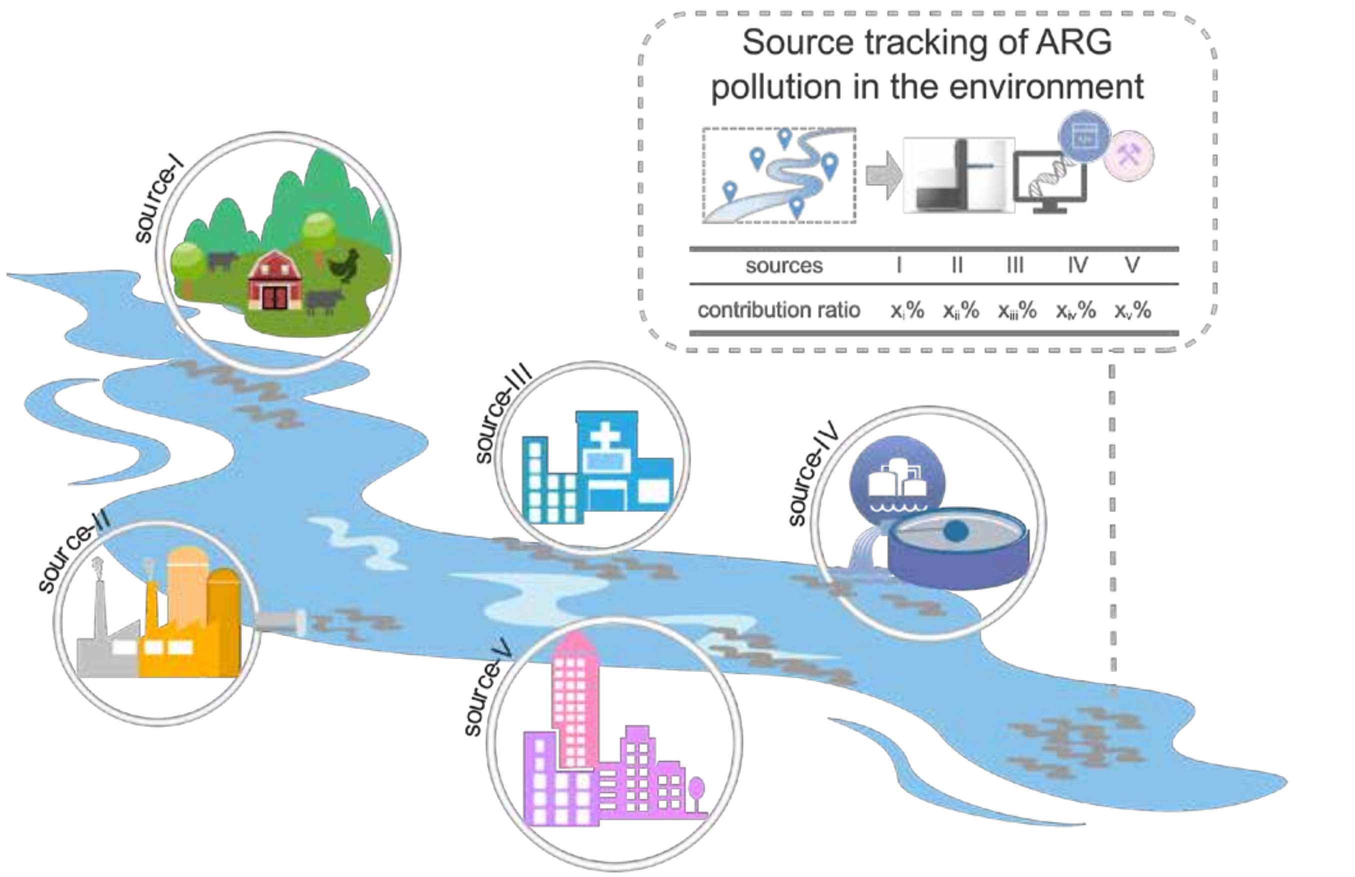


Figure 1. Quantitative source tracking of ARG pollution in the environment[12]

For example, by coupling the detection frequency of specific target ARGs with environmental variables in a particular region, researchers can identify the ARG distribution patterns that distinguish putative sources of ARG pollution (e.g., livestock farm) from a native environment (e.g., river basin).

Current high-throughput sequencing provides a promising approach for efficient source tracking[12]. However, this approach, as a tool for identifying sources of ARG contamination, remains largely unexplored, despite a few large scale surveillances of ARG load in a diversity of environments by metagenomic studies[13,14].
In fact, the distinctive combinations of, potentially, thousands of genetic markers in different environments revealed by metagenomic analysis have a great potential for source discrimination. The major challenge for routine application of such big-data based source-tracking tools is the lack of a robust automated and statistical classification approach. Machine-learning algorithm has been recognized as an efficient tool for pattern recognition in this big-data era. Regarding its potential in source tracking of ARG pollution, the algorithm can use comprehensive ARG profiling of various source environments to train models to distinguish ARG patterns of different source types. The recently developed classification algorithms – RandomForest and SourceTracker, have been successfully applied for microbial source tracking. In particular, unlike traditional source tracking, SourceTracker can model a sample with input from different sources rather than assume the entire sample from a single source[15]. Realizing great potential of the tool, we conducted rigorous analysis to evaluate performance of SourceTracker in quantifying source contribution for environmental ARG pollution[16]. We validated the application of SourceTracker for samples with different anthropogenic impacts, including regional sediment samples with significant gradients of human activity.
Such a combination of metagenomic ARG profiling with cutting-edge machine-learning algorithm in source tracking will facilitate development of novel strategies in tackling the current widespread ARG contamination in the environment. In one recent example, researchers successfully applied the tool to understand the impact of stormwater runoff on ARG load in urban watersheds, as the ARG abundance was significantly higher in urban stream than in base flow during wet weather[17]. They characterized the ARG profile of related environmental compartments under wet weather conditions, and employed SourceTracker to quantify their contributions to the ARG load in an urban stream. They estimated storm drain outfall water as the biggest contribution (>80%) of the high ARG load in the urban stream under wet weather. In addition, similar analysis on street sweepings revealed wash-off from streets as the main contributor of ARGs (>90%) in storm drain outfall water.

RISK ASSESSMENT OF ARGS IN THE ENVIRONMENT – MOBILITY POTENTIAL AND HOST RANGE

Accurate ARG source tracking will provide the basis for downstream efficient source management. Management decisions for ARG containment in the source environment need to consider control priority for target ARGs, since ARGs pose different risk level for human health. Compared with ARGs strictly maintained in specific environmental bacteria, the ARGs with high mobility potential and broad host range should be targeted as high risk ARGs.

Mobile genetic elements, including plasmids, transposons and integrons, as well as integrative and conjugative elements, are efficient vectors to transfer ARGs among bacteria.
In fact, multiple ARGs can be located on the same mobile genetic element, largely facilitating ARG transfer even between distant taxonomic lineages. Moreover, in environment like the wastewater treatment plant and agricultural settings, the presence of antibiotics and other co-selection factors can form a persistent selection pressure for ARGs and their associated mobile genetic elements. In addition to mobility potential, those ARGs with host preference for human pathogens should also be regarded as high risk ARGs.

Human activities have created processes like sewage treatment and manure compost, with high chance of ARG transfer between environmental and pathogenic bacteria. Therefore, evaluating the risk of ARG dissemination requires a comprehensive understanding of ARGs' mobility potential and host range.

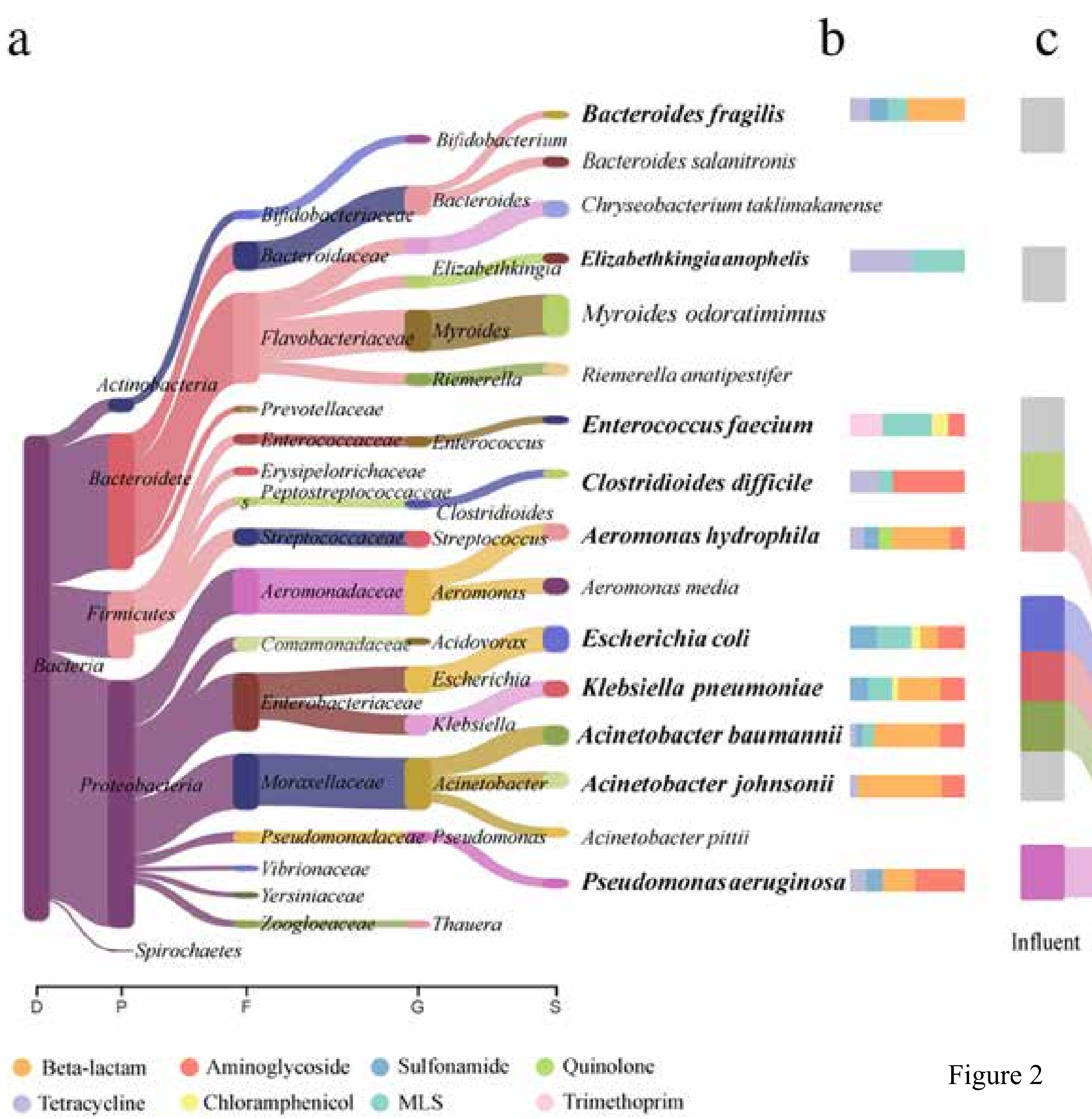


Figure 2.
ARGs carrying pathogens across the wastewater treatment plant compartments[20].
a) The phylogenetic composition and relative abundance of the ARG-carrying pathogens.
b) The diversity and relative abundance of the ARGs (bold in the left panel).
c) Fate of the ARG-carrying pathogens through influent, activated sludge, and effluent.

Figure 2

Previous studies have attempted to reveal the genetic contexts (including the genetic feature of mobility and hosts) of the ARGs with various approaches, including isolation, PCR and high-throughput sequencing.
Although the bias associated to the culture or PCR based methods can be circumvented by current sequencing techniques, deciphering genetic context of the ARG-carrying elements still remains a great challenge.

The frequent repetitive sequences flanking ARGs usually hamper effective assembly of their genetic context. Nevertheless, genetic co-occurrence pattern embedded in metagenomic datasets have been utilized by researchers as the indirect way to track ARGs and their associated genetic features.

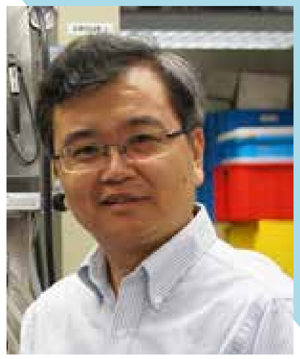
We have successfully applied the statistical tool in disentangling ARG host and mobility in various environment like the wastewater treatment plant, agriculture and drinking water[9,18,19]. In addition, third-generation sequencing technologies provide a great opportunity to directly link the ARGs and their flanking regions. For example, PacBio and Nanopore sequencing can generate long reads which can span most repetitive sequences. In the most recent work[20], we reported the first pipeline based on Nanopore and Illuminat sequencing for rapidly retrieving genetic context of target ARGs, especially for examining ARGs carried by human pathogens along the wastewater treatment process. The results showed that most of the ARGs detected in all compartments of the wastewater treatment plants were carried by plasmids. A broad spectrum of ARGs carried by plasmids was persistent across the wastewater treatment plants. Host tracking showed ARG-carrying bacteria covering broad phylogenetic range, which were still detected in the wastewater treatment plant's effluent (Figure 2). These findings highlights the high risk of ARG dissemination through the wastewater treatment plant discharge into the receiving environment.

Overall, it is apparent that the environment is a large ARG reservoir with a risk for potential dissemination to human pathogens.
In recent years, several international and national governments have announced strategic plan for combating antibiotic resistance within a 'One Health' framework. For example, the government of Hong Kong has committed to manage antibiotic resistance in the 'Strategy and Action Plan on Antimicrobial Resistance 2017-2022'[21].

In parallel with the knowledge developed in humans and animals, comprehension of the environmental antibiotic resistance is urgently needed. As discussed above, we suggest to first perform rigorous regional surveillance of ARG profiles to understand the overall distribution. Based on the surveillance data, the transmission pathways and critical control sources can thus be deciphered. Coupled with risk assessment, management strategies can be properly developed to realize efficient control of antibiotic resistance.

Dr Liguan LI is a postdoc in Environmental Microbiome Engineering and Biotechnology Laboratory in the Department of Civil Engineering at The University of Hong Kong. She obtained her PhD degree from the University of Hong Kong. Dr Li's research interests focus on the environmental dimension of antibiotic resistance, source-tracking of environmental pollution of antibiotic resistance, plasmid transfer and maintenance in microbial communities.

Professor Tong ZHANG is Professor, Environmental Microbiome Engineering and Biotechnology Laboratory in the Department of Civil Engineering at The University of Hong Kong. Professor Zhang obtained his PhD. degree from the University of Hong Kong. His researches include antibiotic resistance genes, biodegradation of emerging pollutants (including antibiotics), biological wastewater treatment, molecular microbial ecology, environmental microbiology and biotechnology. He co-chaired and organized EDAR5, the Fifth International Symposium on the Environmental Dimension of Antibiotic Resistance in June 2019, Hong Kong.



References

(1) U.S Department of Health and Human. Antibiotic resistance threats in the United States. Centers for Disease Control and Prevention. 2019.

(2) Forsberg KJ, Reyes A, Wang B, Selleck EM, Sommer MOA, Dantas G. The Shared antibiotic resistome of soil bacteria and human pathogens. Science. 2012;337(August):1107–11.

(3) Yin X, Deng Y, Ma L, Wang Y, Chan LYL, Zhang T. Exploration of the antibiotic resistome in a wastewater treatment plant by a nine-year longitudinal metagenomic study. Environ Int. 2019;133(November):105270.

(4) Hernando-Amado S, Coque TM, Baquero F, Martínez JL. Defining and combating antibiotic resistance from One Health and Global Health perspectives. Nat Microbiol. 2019;4(9):1432–42.

(5) WHO. Global Action Plan on Antimicrobial Resistance. 2015.

(6) Aarestrup FM, Woolhouse MEJ. Using sewage for surveillance of antimicrobial resistance. Science. 2020;367(6478):630–2.

(7) Hendriksen RS, Munk P, Njage P, van Bunnik B, McNally L, Lukjancenko O, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat Commun. 2019;10(1).

(8) Pärnänen KMM, Narciso-Da-Rocha C, Kneis D, Berendonk TU, Cacace D, Do TT, et al. Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. Sci Adv. 2019;5(3).

(9) Ma L, Li B, Jiang XT, Wang YL, Xia Y, Li AD, et al. Catalogue of antibiotic resistome and host-tracking in drinking water deciphered by a large scale survey. Microbiome. 2017;5(1):154.

(10) Pehrsson EC, Tsukayama P, Patel S, Mejía-Bautista M, Sosa-Soto G, Navarrete KM, et al. Interconnected microbiomes and resistomes in low-income human habitats. Nature. 2016;533(7602):212–6.

(11) Atterby C, Osbjer K, Tepper V, Rajala E, Hernandez J, Seng S, et al. Carriage of carbapenemase and extended-spectrum cephalosporinase-producing *Escherichia coli* and *Klebsiella pneumoniae* in humans and livestock in rural Cambodia; gender and age differences and detection of blaOXA-48in humans. Zoonoses Public Health. 2019;66(6):603–17.

(12) Li LG, Huang Q, Yin X, Zhang T. Source tracking of antibiotic resistance genes in the environment — Challenges, progress, and prospects. Water Res. 2020;185:116127.

(13) Nesme J, Cécillon S, Delmont TO, Monier JM, Vogel TM, Simonet P. Large-scale metagenomic-based study of antibiotic resistance in the environment. Curr Biol. 2014;24(10):1096–100.

(14) Li B, Yang Y, Ma L, Ju F, Guo F, Tiedje JM, et al. Metagenomic and network analysis reveal wide distribution and co-occurrence of environmental antibiotic resistance genes. ISME J. 2015;9(11):2490–502.

(15) Knights D, Kuczynski J, Charlson ES, Zaneveld J, Mozer MC, Collman RG, et al. Bayesian community-wide culture-independent microbial source tracking. Nat Methods. 2011;8(9):761–5.

(16) Li LG, Yin X, Zhang T. Tracking antibiotic resistance gene pollution from different sources using machine-learning classification. Microbiome. 2018;6(1):93.

(17) Baral D, Dvorak BI, Admiraal D, Jia S, Zhang C, Li X. Tracking the sources of antibiotic resistance genes in an urban stream during wet weather using shotgun metagenomic analyses. Environ Sci Technol. 2018;52(16):9033–44.

(18) Ju F, Li B, Ma L, Wang Y, Huang D, Zhang T. Antibiotic resistance genes and human bacterial pathogens: Co-occurrence, removal, and enrichment in municipal sewage sludge digesters. Water Res. 2016;91:1–10.

(19) Ma L, Xia Y, Li B, Yang Y, Li LG, Tiedje JM, et al. Metagenomic assembly reveals hosts of antibiotic resistance genes and the shared resistome in pig, chicken, and human faeces. Environ Sci Technol. 2016;50(1):420–7.

(20) Che Y, Xia Y, Liu L, Li AD, Yang Y, Zhang T. Mobile antibiotic resistome in wastewater treatment plants revealed by Nanopore metagenomic sequencing. Microbiome. 2019;7(1):1–14.

(21) Centre for Health Protection Hong Kong. Hong Kong Strategy and Action Plan on AMR 2017-2022. 2017;94.

ANTIBIOTIC RESISTANCE IN LANDFILL SYSTEMS

Abstract

Landfill systems are important reservoirs for antibiotic resistance genes and antibiotic resistant bacteria. The previous studies on antibiotic resistance in landfill systems were mainly conducted by the researchers from China, USA, Singapore, Japan, Korea, Thailand and Nigeria. The genes conferring resistance to sulfonamide, macrolide-lincosamide-streptogramin, aminoglycoside, beta-lactam, fluoroquinolone, tetracycline and multidrug were the most frequently detected and abundant antibiotic resistance genes types in landfill samples. *Escherichia coli* was selected as a model strain to investigate the antibiotic resistant bacteria in landfill systems and it was commonly multiple antibiotic resistant. However, information on the antibiotic resistant bacteria from landfills is still limited. Both culture-dependent and culture-independent methods should be employed simultaneously to reveal the occurrence characteristics of antibiotic resistant bacteria in landfill systems. Many factors may affect the occurrence and spread of antibiotic resistance genes in landfills, including the composition and properties of municipal solid waste, antibiotics, heavy metals, operational conditions of landfill, mobile genetic elements, etc. The ecological and health risks of antibiotic resistance released from landfill systems need to be assessed in future studies.

> ***Landfill systems are important reservoirs for antibiotic resistance genes and antibiotic resistant bacteria. However, information on the antibiotic resistant bacteria from landfills is still limited. Both culture-dependent and culture-independent methods should be employed simultaneously to reveal the occurrence characteristics of antibiotic resistant bacteria in landfill systems.***

Dr Bing LI, Guangdong Provincial Engineering Research Center for Urban Water Recycling and Environmental Safety, Tsinghua Shenzhen, International Graduate School, Tsinghua University, China

Dr Renxin ZHAO, Tsinghua Shenzhen, International Graduate School, Tsinghua University, China

1. LANDFILL SYSTEMS ARE IMPORTANT RESERVOIRS OF ARGS

Landfill is considered as a potential repository of antibiotics for receiving unwanted and unused drugs, illegal clinical wastes, pet feces, sludge, used baby diapers and toilet papers from clinics, hospitals and households (Eggen et al., 2010). As a consequence, the selection pressures exerted by the presence of antibiotic residuals and other contaminants in the municipal solid waste (MSW) may promote the development and dissemination of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB) in the disposal systems and landfill leachate. Then, the ARGs in the leachate can transfer to the recipient environments and result in serious risk on ecosystem safety and human health.

Polymerase chain reaction (PCR)-based and high-throughput sequencing-based metagenomics analysis methods have been used to characterize the ARG profiles in the landfill sites. The occurrence of diverse and abundant ARGs in landfills indicates that landfill and landfill leachate are important reservoirs of ARGs. Valuable insights have been gained by PCR-based approaches to investigate a few groups of ARGs in landfill leachate. However, these studies only covered a limited number of well-studied ARG types, mainly including the resistance genes of sulfonamide, tetracycline, beta-lactam and fluoroquinolone.

For example, a study from central China showed a high abundance of sulfonamide resistance genes in landfill samples (Song et al., 2016), while beta-lactam and fluoroquinolone resistance genes were prevalent in landfill samples from Shanghai (You et al., 2018). The PCR-based approaches provided a mere snapshot of the ARG profiles in landfills. Using metagenomic analysis approach, Zhao et al. (2018) provided a comprehensive insight of the ARGs occurring in landfill leachate from different cities in China. A total of 526 ARG subtypes belonging to 21 ARG types were identified and the genes conferring resistance to sulfonamide, macrolide-lincosamide-streptogramin, aminoglycoside, multidrug and tetracycline were the most abundant in the 19 leachate samples from 12 cities, highlighting that landfill leachate is an important reservoir of ARGs. In addition, Zhao et al. (2018) found that the ARG abundances in landfill leachate were significantly higher than those in sediments, rivers, activated sludge and anaerobic digestion sludge from sewage treatment plants. The differences in the abundance and composition between landfill leachate and other environmental samples may be associated with the complex formation process and unusual physico-chemical properties of the leachate, which could result in significantly different microbial community structures (Köchling et al., 2015).

The ARGs in landfills may transfer by conjugation, transformation, and transduction into the environmental or pathogenic bacteria through the horizontal gene transfer (HGT) mechanism, promoting the prevalence of ARB in landfill systems and other linked environments. To obtain knowledge for future evaluation and control of potential health risks posed by the disposal of MSW, the occurrence and patterns of ARB in landfill systems have been investigated mainly by culture-dependent methods. When the MSW is dumped into a landfill, the enteric bacteria including *Escherichia coli* originated from the fecal-contaminated wastes can expose to many types of antibiotics. In addition, *E. coli* may interchange their antibiotic resistant properties during a long incubation period inside the landfills.

Therefore, previous studies mostly focused on the antibiotic resistance of *E. coli*. Threedeach et al. (2012) showed that the *E. coli* isolates from landfill leachate highly resisted to tetracycline and cephalothin. High organic loading rate and limited oxygen condition promoted high prevalence of multiple antibiotic resistant *E. coli*. Tetracycline, chloramphenicol and sulfamethoxazole were antibiotics which *E. coli* could develop resistance to under less oxygen available condition (Threedeach et al., 2016). However, information of the ARB from landfills is still limited. Both culture-dependent and culture-independent methods should be employed simultaneously to reveal the occurrence characteristics of ARB in landfill systems.

2. INFLUENCING FACTORS OF ARGS IN LANDFILLS

Due to the highly heterogeneous nature and the complex transformation processes of MSW in landfill systems, many factors may affect the occurrence and spread of ARGs in landfills, including mobile genetic elements (MGEs), antibiotics, heavy metals, other physico-chemical parameters (pH, moisture, conductivity, TOC, COD, BOD5, DOC, TN, NH3-N, NO3–/NO2–-N, TP, PO43–, SO42–, Cl–, etc.) and the characteristics associated with landfills. Among these factors, some studies have shown that MGEs are the determining factors contributing to the occurrence of ARGs in landfills. For example, Yu et al. (2016) found that all the three detectable sul genes significantly correlated to the genetic markers of integrons, plasmids and transposons, implying the HGT of ARGs facilitated by various MGEs might take place in the landfill environment. Wang et al. (2021) reported the positive correlations between ARGs and IntI1 in landfill leachate, suggesting that the variation of ARGs might be mediated by IntI1 and the HGT of ARGs might frequently occur in leachate.

Generally, the abundant and diverse ARG types were associated with the antibiotics used extensively as human or veterinary medicine. ARGs may enter into landfills directly or develop over time in the presence of antibiotic residues in MSW, thus possibly causing the prevalence of ARGs in landfill leachate. Su et al. (2017) observed the abundance of sulfonamide resistance genes (sul1 and sul2) were in accord with the antibiotic levels in the leachate. Yu et al. (2016) reported that most studied antibiotics were positively correlated to the ARGs, and high levels of antibiotics forced severe selection pressure in the closed landfill environment.

However, previous studies also suggested that the direct selection pressure of antibiotics in landfills was not a key factor shaping the ARG profiles.
Although antibiotics in the leachate had relatively high concentrations, no significant correlations

were found between most target antibiotics and their corresponding ARGs in landfill leachate (Zhao et al., 2018). The types and levels of ARGs and antibiotics did not depend on each other owing to different environmental fate and transport mechanisms of antibiotics and ARGs in the leachate (Wu et al., 2015, Yi et al., 2017). The fate of antibiotics tends to rely on hydrolysis, sorption, desorption, and chemical/biological degradation processes, while the fate of ARGs is likely to rely on bacterial host type (Wu et al., 2015, Yi et al., 2017). Therefore, the relationship between ARGs and the antibiotic concentrations is very complex and the enrichment of ARGs may not be only contributed by the antibiotic selection pressure.

During the lifespan of a landfill, the hydrology, operation conditions of landfill (e.g. drainage rate and disposal rate), the amount, composition and properties of MSW may change continuously (Kjeldsen et al., 2002). All these factors can affect leachate quantity, leachate quality, the microbial community and ARGs in the leachate. et al. (2018) revealed the negative correlations between water quality parameters (TN, NH_3-N, TP, COD, TOC and EC) and the abundance of ARGs in landfill leachate. Yu et al. (2016) found that the carbon-related parameters (COD, BOD5 and DOC) held a decreasing tendency with the landfill age and were significantly negatively correlated to the ARGs.

In addition, Song et al. (2016) found the abundance of sul1 and teto were positively correlated with moisture content in MSW. Physico-chemical conditions within the refuse correlated to ARGs and this suggested that environmental factors might impact the distribution of ARGs in landfilling systems. Further, the presence of the heavy metals can drive the spread of ARGs in landfills in the long run. It is known that heavy metal and antibiotic resistance are frequently linked in the same MGEs, therefore long-standing co-selection pressure imposed by metal might increase the dissemination of ARGs among leachate (Wu et al., 2015).

The landfill leachate characteristics can be affected by various factors, such as landfill age, waste type and composition, landfill design, rainfall, climate, and decomposition degree (Reshadi et al., 2020). Among these factors, the landfill age is considered as a determinant factor influencing the leachate composition and thus can exert a powerful influence on the concentrations of antibiotics and heavy metals, as well as the ARGs in the leachate. Zhao et al. (2018) reported that landfill age was positively correlated with the total abundance of ARGs in landfill leachate. Yi et al. (2017) noted that old landfill site served as important reservoir of ARGs.

However, Wang et al. (2015) reported that the abundance of sul1 in landfill leachate was negatively correlated to the landfill ages, suggesting that the ARGs decreased along time addition. Regardless of whether present in living or dead cells, ARGs, which could move between microbes via HGT, can survive in the landfills for years without the presence of their live hosts even after the selective pressure responsible for their formation has been removed (Song et al., 2016, Yu et al., 2016). Therefore, landfill age can exert a powerful influence on the abundance of ARGs in disposal systems and the leachate. Overall, the differences of ARG behavior and fate in different landfills could be attributed to various factors, such as refuse type, landfill age, landfilling patterns, climate conditions and physico-chemical properties of each landfill site.

Although the environmental factors play important roles in the presence of ARGs, it is noteworthy that microbes are the hosts of ARGs. It is well known that environmental conditions closely link to the variations of microbial community structure, which is considered to be an important factor promoting the enhancement and spread of ARGs (Novo et al., 2013). Previous studies have suggested that ARG profiles are significantly correlated with microbial community composition (Su et al., 2017; Zhao et al., 2018). This indicated that microbial community composition may be the determining factor of ARG compositions in landfills.

3. CONCLUSIONS

In summary, landfill systems and landfill leachate are important sources of antibiotic resistance. The occurrence of ARGs in landfills may be affected by various factors including physical, chemical and biological factors. The ecological and health risks of antibiotic resistance released from landfill systems need to be assessed in future studies and more effective management strategies are required to be implemented.

Dr. Bing LI is an associate professor in Tsinghua Shenzhen International Graduate School, Tsinghua University, China. In 2016, he won the “First Prize in Natural Science Award from the Ministry of Education” and the “State Environmental Protection Young Talent in Professional Technology Award”. In 2019, Dr. Li was nominated as the Editorial Board Member of Applied Microbiology and Biotechnology. His research interests mainly focus on the application of high-throughput sequencing to investigate the fates of ARGs and ARB in sewage treatment plants, landfills as well as natural environments. He has published 77 papers on the top journals including ISME J and Microbiome etc.

Renxin ZHAO received his PhD. degree in Environmental Science and Engineering from Tsinghua University. He is currently a postdoctoral researcher in Dr. Bing Li's laboratory at Tsinghua Shenzhen International Graduate School, Tsinghua University. Dr. Zhao's main research interests are the development and spread of antibiotic resistance in the environment based on metagenomic methods. He has published 15 papers in Water Research, Science of The Total Environment, Journal of Hazardous Materials, Frontiers in Microbiology, Environment International, etc.

References

Eggen, T., Moeder, M., Arukwe, A., 2010. Municipal landfill leachates: a significant source for new and emerging pollutants. Sci.Total Environ. 408 (21), 5147–5157.

Kjeldsen, P., Barlaz, M.A., Rooker, A.P., Baun, A., Ledin, A., Christensen, T.H., 2002. Present and long-term composition of MSW landfill leachate: a review. Crit. Rev. Environ. Sci. Technol. 32, 297–336.

Köchling, T., Sanz, J.L., Gavazza, S. Florencio, L., 2015. Analysis of microbial community structure and composition in leachates from a young landfill by 454 pyrosequencing. Appl. Microbiol. Biotechnol. 99, 5657–5668.

Novo, A., André, S., Viana, P., Nunes, O.C., Manaia, C.M., 2013. Antibiotic resistance, antimicrobial residues and bacterial community composition in urban wastewater. Water Res. 47, 1875–1887.

Reshadi, M.A.M., Bazargan, A., McKay, G., 2020. A review of the application of adsorbents for landfill leachate treatment: Focus on magnetic adsorption. Sci. Total Environ. 731, 138863.

Song, L., Li, L., Yang, S., Lan, J., He, H., McElmurry, S.P., Zhao, Y., 2016. Sulfamethoxazole, tetracycline and oxytetracycline and related antibiotic resistance genes in a large-scale landfill, China. Sci. Total Environ. 551–552, 9–15.

Su, Y., Wang, J., Huang, Z., Xie, B., 2017. On-site removal of antibiotics and antibiotic resistance genes from leachate by aged refuse bioreactor: effects of microbial community and operational parameters. Chemosphere 178, 486–495.

Threedeach, S., Chiemchaisri, W., Chiemchaisri, C., 2016. Fate of antibiotic resistant *E. coli* in anoxic/aerobic membrane bioreactor treating municipal solid waste leachate. Int. Biodeter. Biodegr. 113, 57–65.

Threedeach, S., Chiemchaisri, W., Watanabe, T., Chiemchaisri, C., Honda, R., Yamamoto, K., 2012. Antibiotic resistance of *Escherichia coli* in leachates from municipal solid waste landfills: comparison between semi-aerobic and anaerobic operations. Bioresour. Technol. 113, 253–258.

Wang, Y., Tang, W., Qiao, J., Song, L., 2015. Occurrence and prevalence of antibiotic resistance in landfill leachate. Environ. Sci. Pollut. Res. 22, 12525–12533.

Wang, P., Wu, D., You, X., Su, Y., Xie, B., 2020. Antibiotic and metal resistance genes are closely linked with nitrogen-processing functions in municipal solid waste landfills. J. Hazard. Mater. 403, 123689.

Wu, D., Huang, Z., Yang, K., Graham, D., Xie, B., 2015. Relationships between antibiotics and antibiotic resistance gene levels in municipal solid waste leachates in Shanghai, China. Environ. Sci. Technol. 49, 4122–4128.

Yi, X., Tran, N.H., Yin, T., He, Y., Gin, K.Y.-H., 2017. Removal of selected PPCPs, EDCs, and antibiotic resistance genes in landfill leachate by a full-scale constructed wetlands system. Water Res. 121, 46–60.

Yu, Z., He, P., Shao, L., Zhang, H., Lü, F., 2016. Co-occurrence of mobile genetic elements and antibiotic resistance genes in municipal solid waste landfill leachates: a preliminary insight into the role of landfill age. Water Res. 106, 583–592.

Zhao, R., Feng, J., Yin, X., Liu, J., Fu, W., Berendonk, T.U., Zhang, T., Li, X., Li, B., 2018. Antibiotic resistome in landfill leachate from different cities of China deciphered by metagenomic analysis. Water Res. 134, 126–139.

MICROBIOLOGICAL CHARACTERIZATION OF WASTEWATERS IN CHOLERA ENDEMIC AREAS OF BENIN

Abstract

Wastewater discharged into the environment without treatment is a danger to human health in general and especially in poor countries, as it is responsible for the high mortality of children from diarrheal diseases. This wastewater is a prime site for the transmission of antibiotic resistance genes. In Benin, even geographically limited analyses show high rates of resistance to common drugs against cholera, *Escherichia coli* and *Salmonella spp*. Our work suggests that: 1) fighting antibiotic resistance would require serious efforts to invest in infrastructure to recycle human and animal waste and to develop access to clean water in Benin, and 2) efforts for better antibiotic management at the individual, hospital or farm level may have little effectiveness without first treating the environment, where bacteria transfer resistance genes.

Water management is also one of the necessary bases for the implementation of infection control in health care facilities, protecting both caregivers and patients from the spread of COVID-19 as well as of antimicrobial resistant infections.

The impact of water and sanitation on diarrheal diseases and overuse of antibiotics has been well analyzed by Jim O'Neill's AMR Review in the UK, in work that has been authoritative worldwide.

> *"Benin continues to be an endemic zone for typhoid fever and cholera due to the non application of the national hygiene and sanitation policy. Epidemics occur there every year. The areas at risk are typically peri-urban slums that lack basic sanitation infrastructure and where drinking water supply and sanitation conditions cannot be ensured. Sustainable water, sanitation and hygiene programs must be carried out as a priority in regularly affected communities."*

Professor Bawa Boya, PhD, Microbiology and Molecular Biology, Laboratory of Biology and Molecular Typing in Microbiology (LBTMM), Department of Biochemistry and Cell Biology, Faculty of Sciences and Techniques, University of Abomey-Calavi, Cotonou, Benin.

Professor Theodora A. Ahoyo, PhD, Lecturer in Microbiology, Physiology and Hygiene, Human Biology Engineering, Ecole Polytechnique d'Abomey-Calavi, Benin.

INTRODUCTION

Water can be an important means of spreading diarrheal diseases when contaminated with pathogens. According to the World Health Organization (WHO), about 90% of children who die each year from diarrhea contract it due to poor water quality and poor hygiene and sanitation conditions[1]. Lack of sanitation is a major cause of morbidity and a threat to human and animal health[2,3].

According to the WHO[4], 80% of the diseases affecting the world's population are linked to water pollution.

Water-borne diseases have been responsible for vast epidemics of dysentery, typhoid fever, cholera and others according to George and Servais[5]; with high mortality among populations in resource-limited countries. Vulnerable and deprived populations in disadvantaged neighborhoods are the most affected[6]. These diseases are most often transmitted by fecal-oral route, either through consumption of food contaminated by water, or through bathing or contact with recreational waters[5]. Wastewaters from cities in Benin are discharged without prior treatment into gutters that also carry rainwater run-off to river beds.

This wastewater is also used by local residents, especially for irrigation of market gardens[7]. It is in this context that we wanted to search for pathogenic bacteria linked to peri-faecal matter in the endemic areas of cholera in Benin.

MATERIALS AND METHODS

The study was carried out in the cholera endemic areas of Benin from June to August 2020. Wastewater samples were collected in the communes of: Abomey-Calavi, Dassa-Zoumé, Djougou, Cotonou, Porto-Novo, Sô-Ava, Parakou, Sèmè-Kpodji.

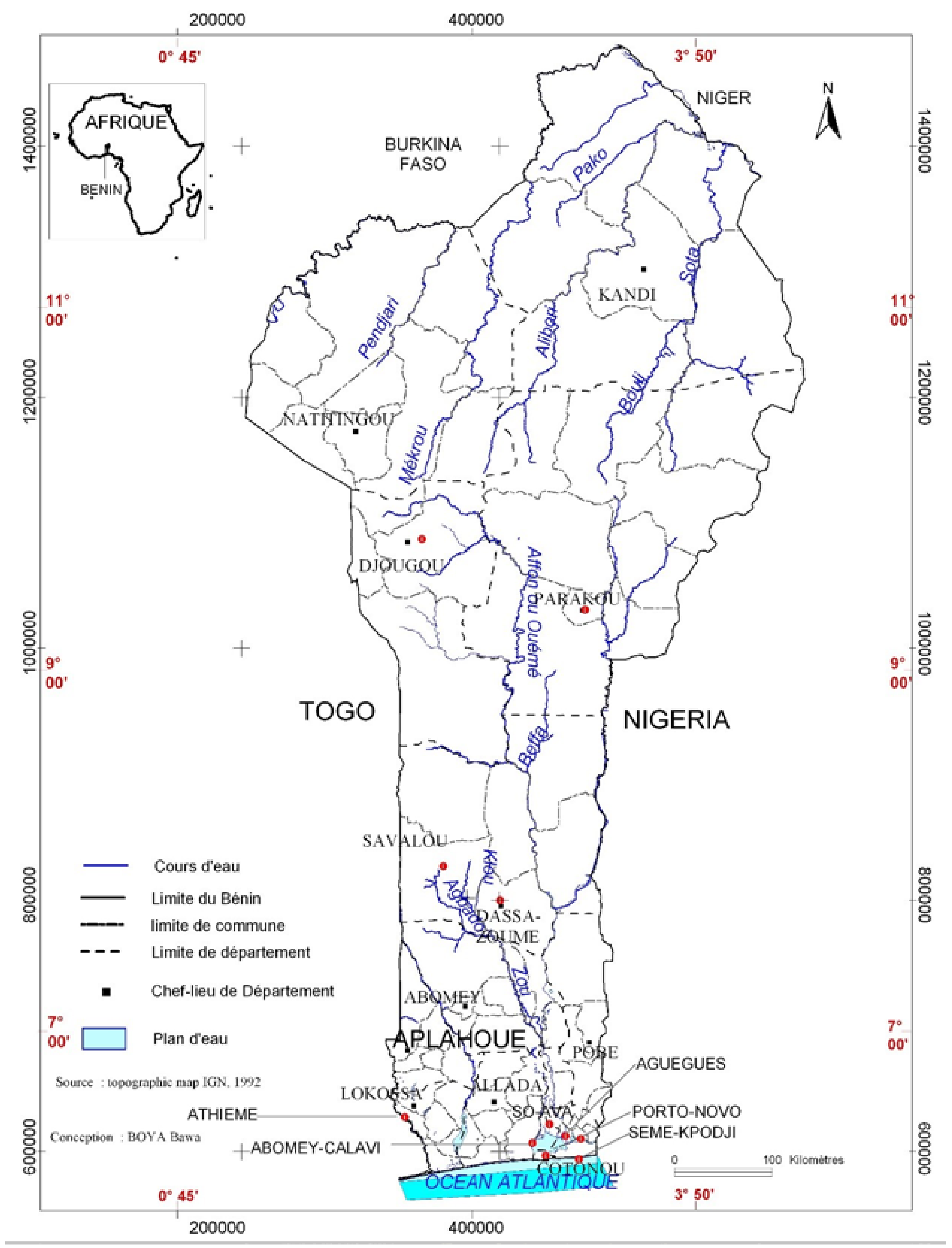


Figure 1: Map of Benin showing the sampled areas marked with red dots.

1.1. Microbiological Sampling and Analysis

Water samples were collected in 500ml borosilicate flasks with strings following the techniques described by Rodier[8]. The vials intended for bacteriological analysis were sterilized at 121°C for 20 min in an autoclave. The collected water samples were then stored at 4°C in a cooler and transported to the laboratory for analysis. A total of 160 water samples were taken, with 20 samples per commune. The pH of the samples is measured with an electronic pH meter (Hanna's HI 96107 instruments).

Images: Photos of water taken in Cotonou by B. Boya

(a) Tokpa

(b) Ladji.

(c) Ahouansori

(d) Djidjè

The fecal hazard indicator bacteria *Escherichia coli*, *Salmonella* and *Vibrio* were tested on the sites. Serotyping of *Vibrio cholerae* strains was performed by slide agglutination test with anti-O1 and O139 sera. Multiplex PCR was used to differentiate between *Vibrio cholera*

1.2. Antibiotic susceptibility of strains isolated from wastewater samples

The antibiogram was performed with nine (9) antibiotic discs: Amoxicillin/Clavulanic Acid (AMC, 30µg), Oxytetracycline (OT, 30µg), Sulfamethoxazole-trimethoprim (SXT, 25/µg), Ceftazidime (CAZ, 30µg), Gentamicin (G, 10µg), Doxycycline (DOX, 30µg), Erythromycin (E, 15µg); Ofloxacin (OFX : 10µ g) and Ceftriaxone (CTR, 30 µg).

The results were read and interpreted according to the criteria of the Antibiogram Committee of the French Society of Microbiology 2019.

RESULTS

2.1. Physico-chemical parameter

Average pH values range from 6.11±0.03 to 7.52±0. Average temperature values range from 27.85±0.1 to 32.91±1.7°C.

2.2. Microbiological quality of household wastewater.

Table 1 presents the set of microbial strains isolated from the wastewater samples. Out of 160 wastewater samples analyzed, 210 micro-organisms were isolated.

Isolated bacteria	Number (N)	Percentage (%)
Vibrio cholerae	54	25.71
Other *Vibrio*	22	10.47
Salmonella spp	58	27.62
Escherichia coli	51	24.28
Other micro-organisms	25	11.90
Total	210	100.00

Table 1: Main micro-organisms isolated from wastewater[2,3]. Antibiotic resistance of microbial strains isolated from waste water

2.3.1 Antibiotic resistance of *Vibrio cholerae* strains isolated from wastewater

All strains showed resistance to Amoxicillin + clavulanic acid, Ceftazidime and Oxytetracycline. Resistance to Sulfamethoxazole-trimethoprim and doxyxycline was 75.86%.
Figure 2 shows the results.

2.3.2. Antibiotic resistance of *Escherichia coli* strains isolated from wastewater

All strains isolated showed resistance to Amoxicillin + clavulanic acid, Ceftazidime and Oxytetracycline. Resistance to Sulfamethoxazole-trimethoprim is 75.86% and 88% to Doxycycline.
Figure 3 shows the results.

2.3.3. Antibiotic resistance of *Salmonella spp* strains isolated from wastewater

The resistance of isolated *Salmonella spp* strains varies with antibiotics. All strains showed 100% resistance to Amoxicillin + clavulanic acid, Ceftazidine, Sulfamethoxazole-trimethoprim 75.86% to Doxycycline. **Figure 4** shows the results.

DISCUSSION

Nowadays wastewaters are frequently reused, either for various purposes or for groundwater recharge. Water can therefore act as a vector for potentially dangerous microbiological agents such as *Salmonella spp*, *Vibrio cholerae* and *Escherichia coli*[9]. The control and monitoring of water quality, especially wastewaters, is becoming essential[9].
The bacteriological analyses we carried out on run-off water from cholera endemic areas in Benin revealed a significant variation in the microbial load of the bacteria studied. Open defecation is still a common practice among the populations in the study area and confirms the existence of the fecal threat. Benin continues to be an endemic zone for typhoid fever and cholera due to the non-application of the national hygiene and sanitation policy. Epidemics occur there every year. The areas at risk are typically peri-urban slums that lack basic sanitation infrastructure and where drinking water supply and sanitation conditions cannot be ensured. Sustainable water, sanitation and hygiene programs must be carried out as a priority in regularly affected communities.

The 75% doxycycline resistance of *Vibrio cholerae* strains is a cause for concern. This situation could be the probable result of the current protocol that proposes doxycycline chemoprophylaxis administered to all accompanying patients and health personnel, for whom there were no contraindications in Benin, Makoutodé et al[10]. Resistance to Trimethoprim/sulfamethoxazole is 75.86% for environmental strains; this molecule is often prescribed in the treatment of gastroenteritis and in chemo prophylaxis in HIV-infected persons. According to Opintan et al.[11], in Ghana, genotypic characterization of *Vibrio cholerae* revealed an SXT transposon and a class 29 integron.
These results show that this antibiotic should no longer be used in the treatment of cholera. Indeed, taking this drug would contribute to the selection and dissemination of emerging resistant strains in the population. In addition, the use of sulfona-

Amoxicillin/Clavulanic Acide (AMC, 30µg), Oxytétracycline (OT, 30µg), Sulfaméthoxazole-trimethoprime (SXT, 25µg), Ceftazidime (CAZ, 30µg), Gentamicine (G, 10µg), Doxycycline (DOX, 30µg), Erythromycine (E, 15 µg), Ofloxacin (OFL, 10µg), Ceftriaxone (CTX, 30µg)

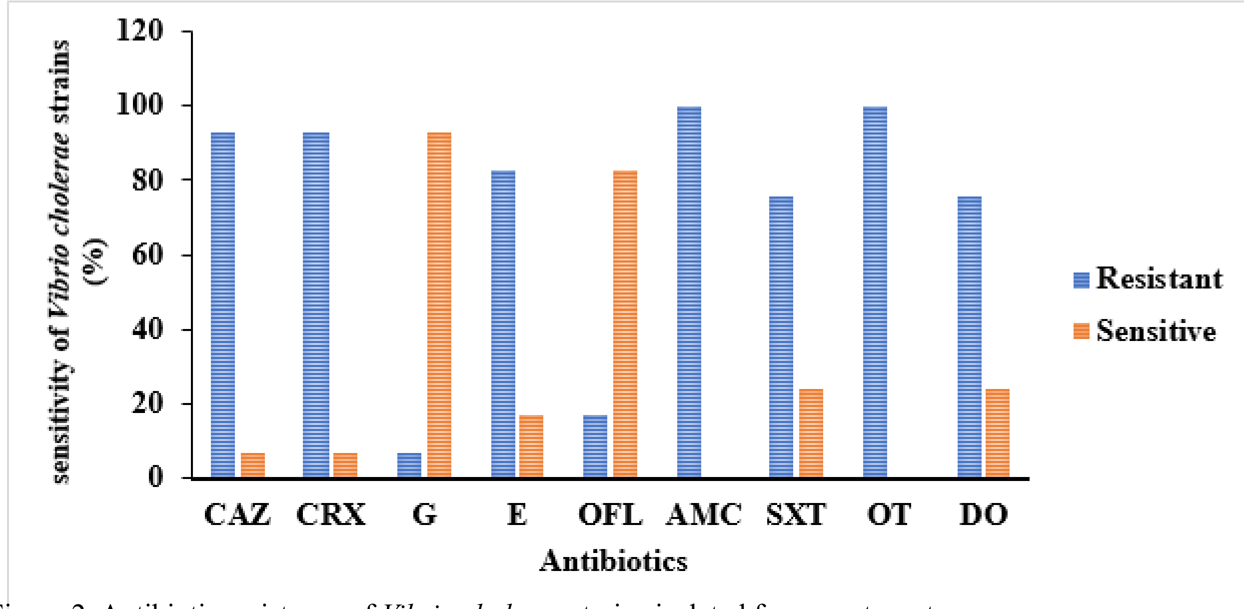


Figure 2: Antibiotic resistance of *Vibrio cholerae* strains isolated from waste water

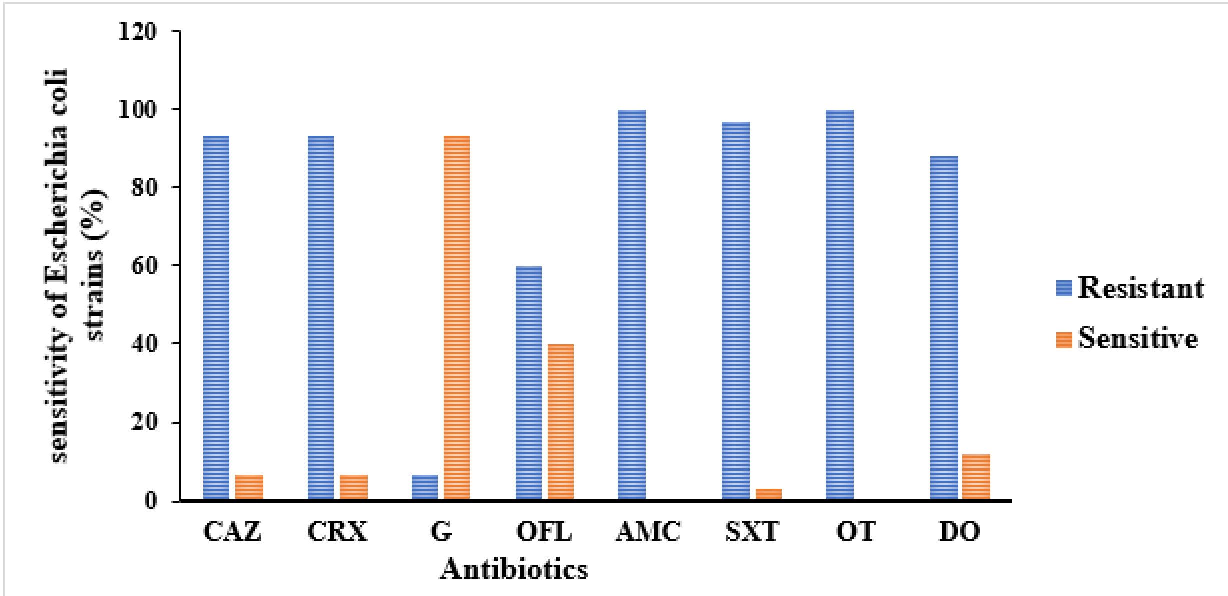


Figure 3: Resistance of isolated *Escherichia coli* strains to antibiotics.

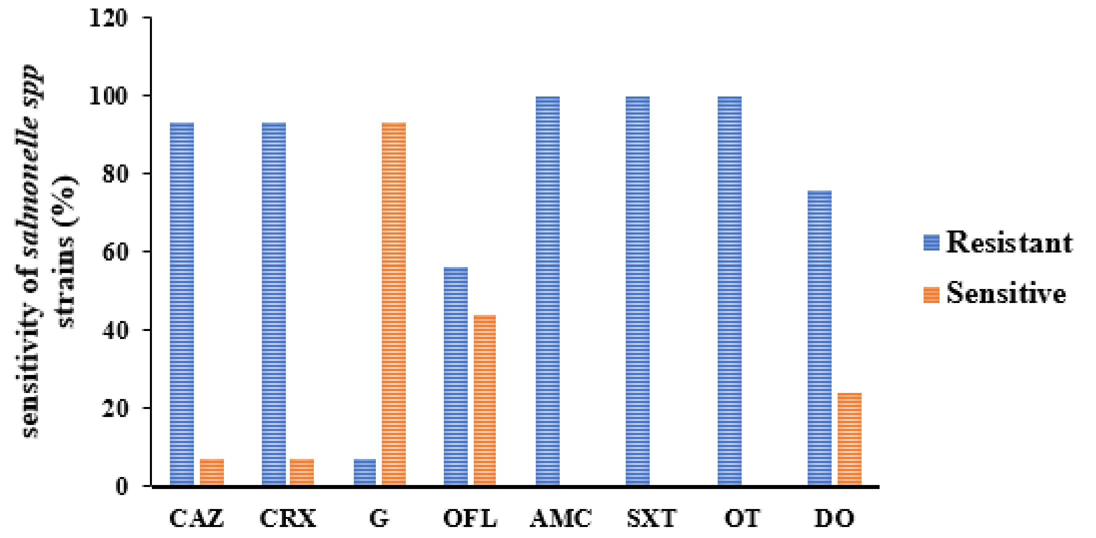


Figure 4: Antibiotic resistance of *Salmonella spp* strains isolated from water.

mide-based molecules in the treatment of malaria could be the cause of cross-resistance[12]. This high resistance to doxycycline and Trimethoprim/sulfamethoxazole is also found in *Salmonella spp* and *Escherichia coli*. Bacteria can develop resistance to antibiotics, which share similar genetic structures[13]. Although they do not present a direct therapeutic challenge, these acquisitions of resistance may be problematic given the ability of *Vibrio* to share their genetic information[13].

In the environment or in the digestive tract, these resistances can be transmitted to bacteria with which they are in contact and make the treatment of infections by other bacteria more difficult[13].

CONCLUSION

The results obtained in this study indicate that stormwater wastewater is heavily polluted with microorganisms that are indicators of fecal contamination. This pollution is remarkable at the collector level. These results showed a diversity and distribution of strains of *Vibrio cholerae*, *Salmonella spp* and *Escherichia* in the study areas. The proportion of multi-resistant bacteria resistant to commonly prescribed antibiotics is high and cause for concern. Sanitation and the extension of hygiene measures around these water points to prevent recurrent epidemiological episodes in the city, especially during rainy seasons, should be promoted.

Acknowledgements - We thank Professor Lamine Baba Moussa and all the staff of his laboratory for their support.

Dr Bawa Boya is Doctor in Microbiology and Molecular Biology from the University of Abomey Calavi. Bachelor's degree in Microbiology and Application (2012), Master's degree in Microbiology and Food Technology (2016), PhD (2020), at the National University of Abomey Calavi. Co-author of eight publications and communications. In 2019, he won the prize for best communication displayed at the fourth edition of the CAMES Scientific Days. From 2011 to 2014, he was granted the Excellence Scholarship from the Government of Benin, University of Abomey-Calavi, Benin.

Dr. Théodora Angèle Ahoyo is a professional hygienist from Benin working on Infection Prevention and Control (IPC). She is the National Focal Point for Patient Safety in Benin. She is also a lecturer and researcher at the University of Abomey-Calavi (UAC), Associate Professor, Doctor of Microbiology and Epidemiology. She obtained a Master's degree in Hospital Hygiene and a PhD in Medical Microbiology. She is also an international expert in IPC against Infections contracted in healthcare settings. She holds a certificate in Patient Safety Management in Healthcare Facilities.

References

(1) Stratégie de l'OMS sur l'eau, l'assainissement et l'hygiène 2018-2025, Genève (WHO Water, Sanitation and Hygiene strategy 2018-2025, Geneva)

(2) El-Kettani S. et Azzouzi EM. Prévalence des helminthes au sein d'une population rurale utilisant les eaux usées à des fins agricoles à Settat (Maroc). Environnement, Risques et Santé. (2) (2006) pp. 99-106.

(3) Talouizte H., Merzouki M., ElOuali Lalami A., Bennani L., Benlemlih M. Evolution de la charge microbienne de la laitue irriguée avec les eaux usées urbaines de la ville de Fès au Maroc, Tribune de l'eau. 642(2007).

(4) Guidelines for drinking-water quality. Vol.1. Recommandations, 3rd, Ed. World Health Organization. Geneva (2004).

(5) George I. et P. Servais. Sources et dynamique des coliformes dans le bassin de la Seine. Centre National de la Recherche Scientifique, Paris, France, (2002), 46 p.

(6) Sy I, Koita M, Traoré D, Keita M, Lo B., Tanne M, Cissé G. Vulnérabilité sanitaire et environnementale dans les quartiers défavorisés de Nouakchott (Mauritanie) : analyse des conditions d'émergence et de développement des maladies en milieu urbain sahélien. [VertigO] Revue en Sciences de l'Environnement, 11(2), 2011 : 17p.

(7) Legba CS, Yabi I, Azonhe T, Osseni AA. Analyse des Déterminants du Choléra dans la Ville de Djougou au Bénin. European Scientific Journal 2017; Vol.13, No.18 ISSN: 1857 – 7881

(8) Rodier J., Bazin C., Broutin J.P., Chambon P., Champsaur H., Rodin L, L'analyse de l'eau : eaux naturelles, eaux residuaires, eau de mer, 8e édition. Dunod, Paris, France (1996).

(9) Lalami A. El Ouali., Zanibou A., Bekhti K., Zerrouq F., Merzouki M. Contrôle de la qualité microbiologique des eaux usées domestiques et industrielles de la ville de Fès au Maroc J. Mater. Environ. Sci. 5 (S1) (2014) 2325-2332

(10) Makoutode, M.F., Diallo, V., Mongbo, E., Guevart, E. and Bazira, L. La riposte à l'épidémie de choléra de 2008 à Cotonou. Santé Publique, (2010), 22, 435-425. https://doi.org/10.3917/spub.104.0425.

(11) Opintan JA, Newman MJ, Nsiah-Poodoh OA, Okeke IN.,. *Vibrio cholerae* O1 from Accra, Ghana carrying a class 2 integron and the SXT element. J Antimicrob Chemother.62 (5), 2008, 929-3.

(12) Adabi M, Bakhski B, Goudarzi H, Zahraei SM, Pourshafie MR. Distribution of class 1 integron and sulfamethoxazole trimethoprim constin in *Vibrio cholerae* isolated from patients in Iran. Microb Drug Resist. 15(3), 2009: 179-84.

(13) Briet A., Helsens N., Delannoy S., Debuiche S., Brisabois A., Midelet G., Granier S.A. NDM-1-producing *Vibrio parahaemolyticus* isolated from imported seafood. J Antimicrob Chemother (2018).

(14) AMR REVIEW, Jim O'Neill, UK, Capstone Report : « The Impact of Water and Sanitation on Diarrhoeal Diseases Burden and Over-prescription of Antibiotics.

AMR IN AQUACULTURE ENVIRONMENT

SECTION II

PERSISTENCE OF ANTIBIOTIC-RESISTANCE GENES IN AQUACULTURE ENVIRONMENT

Abstract

Bacteria become antibiotic-resistant by acquisition of antibiotic-resistance genes. Aquaculture is one of the hot-spots of antibiotic use, making it a place where antibiotic-resistance genes are developed and selected. These genes can be transferred to various bacteria and spread further into the aquatic environment.

The resistance genes found in humans and animals could also be detected in aquaculture environment, suggesting transfer of the resistance genes among terrestrial and aquatic bacteria. And it has recently been shown that aquatic commensal bacteria possess unique resistance genes. We should consider that the origins of resistance genes, and consequent exposure risk, not only concern pathogenic/terrestrial bacteria, but also aquatic bacteria. To decrease exposure risk to the resistance genes, we should pay attention to aquatic environment, aquatic substances, and humans in aquaculture.

> “*In order to produce healthy and safe aquaculture products, control of feeding amount and prevention of pollution in fishing grounds are essentially needed as well as appropriate administration of antibiotics. These strategies decrease diseases in fish, and then leads to reduction in the use of antibiotics.*”

Professor Satoru Suzuki, Center for Marine Environmental Studies, Ehime University, Matsuyama, Japan

Aquaculture systems differ from country to country. Freshwater pond aquaculture is the main system in inland areas of China, Eastern Europe and North America, whereas net-pen marine aquaculture is frequently carried out in Norway, Chile and Japan. In any case, antibiotics are still frequently used, resulting in the direct spread of antibiotic compounds into rivers and sea. Thus, as expected, aquaculture is among the sources of contamination of natural waters with antibiotics, which entails the development of antibiotic resistant bacteria and antibiotic-resistance genes (Cabello et al., 2013).

In case of freshwater, human and animal enteric bacteria contaminate aquaculture water and survive there for a long time, becoming a source of resistance gene exposure for humans (Antunes, et al., 2018; Klase, et al., 2019). Various resistance genes, and mobile genetic elements that can transfer resistance genes to other cells, are detected in biofilms on the surface of river beds and pipelines (Balcázar et al., 2015).

The viscous biofilm substances are reservoirs of resistance genes in aquaculture facilities. Biofilms are generally main hot spots of cell-to-cell horizontal gene transfer in aquatic environments (Abe et al., 2020).

Tropical Asian countries have been historically practicing integrated aquaculture-agriculture farming system, where livestock manure is directly transported to fish ponds and to vegetable and rice fields. The manure contributes to the eutrophication of pond water, enhancing phytoplankton growth. This is good recycling farming practice; yet the heavy use of antibiotics in livestock develops antibiotic resistance in enteric bacteria and water bacteria. Therefore such farming sites are a potential origin of antibiotic-resistance genes; in other words, it is a “risk incubating environment” or “bazaar of resistance genes” (Suzuki and Hoa, 2012).

The resistant bacteria and the resistance genes initially arise in the intestinal tract of animals as a result of exposure to high concentrations of various antibiotics.

Next, horizontal gene transfer occurs among various bacteria in the environment surrounding the farm. The resistance genes persist and spread among environmental bacteria through acquisition and recombination, Finally, the resistance genes move to other environments via water use and food supply. Freshwater pond aquaculture is closely connecting agriculture, food and human daily life.

The situation in marine aquaculture is different from that in freshwater. Microflora in seawater is quite different from freshwater in terms of category and physiology, considering that most of commensal bacteria in seawater are non-culturable or yet-to-be cultured. Human enteric and pathogenic bacteria cannot survive in the sea due to the properties of the seawater environment; low temperature, low organic matter concentration, high salt concentration and so on.

Although researches on antibiotic-resistant bacteria started in the 1950’ in Salmonella, the first evidence of multi-drug resistance plasmid was reported in fish pathogenic bacteria from Japanese marine aquaculture (Aoki, et al., 1971), which plasmid then evolved with time through various countries and various bacteria including human enteric bacteria (Fricke, et al., 2009). This suggests that transferable plasmids are transported even among marine and terrestrial environments. The fact also suggests horizontal gene transfer and circulation of the resistance genes among diverse microbes in a wide variety of environments.

Most researches on antibiotic resistance, in the early age of marine aquaculture, were performed for isolated fish pathogens. Recent metagenomic approaches have been revealing distribution pro-

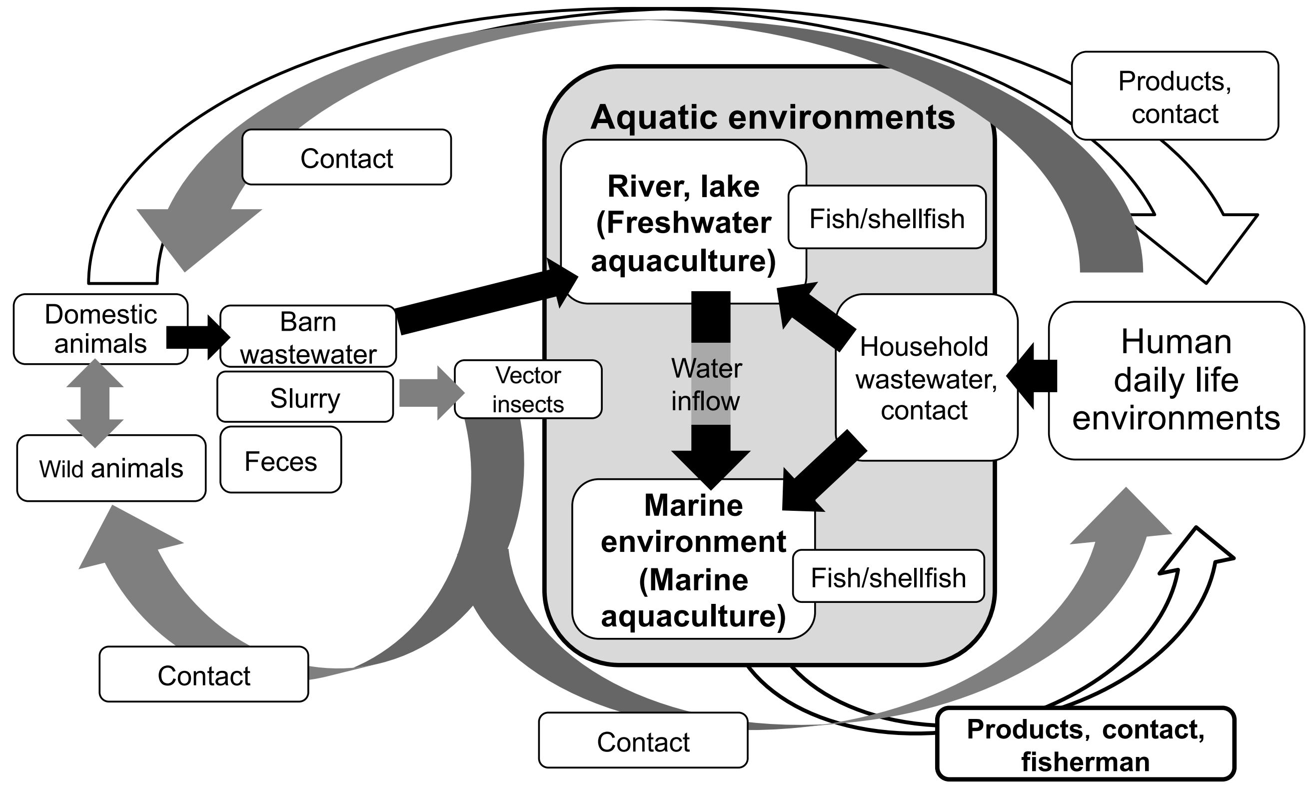


Figure 1
Suspected exposure route of antibiotic resistant bacteria and antibiotic resistance genes with focus on aquatic environments. Black arrow, inflow; grey arrow, contact and white arrow, intake/contact. (Modified from Gebreyes et al., 2017)

files of resistance genes among all microbial communities including non-culturable bacteria. This is what is called "resistome" analysis. Sulfonamides and tetracyclines have been used worldwide in marine aquaculture, providing a selective pressure for bacteria in fish intestines and seawater. Especially, tetracyclines are still frequently used worldwide, and tetracycline-resistance genes, namely tet, persist for long time in sediment beneath the aquaculture fishing ground (Tamminen, et al., 2011).

The fish feces contribute in supplying resistance genes into the sediment (Muziasari, et al., 2017). The occurrence profiles of tet in aquaculture seawater differ among countries (Suzuki, et al., 2019).

The sulfonamide resistance genes, namely sul, are also detected in a variety of water environments. It follows that the resistance genes with a long history, such as tet and sul, disseminate and persist in freshwater and marine environment. Sul3 is a rare sul gene in human clinical care, but it is reported to be abundant in marine non-culturable bacterial community (Suzuki et al., 2013). Recent report showed that new sul4 was found in river originating from Chloroflexi (Razavi et al., 2017) which belongs to an ancient division including various marine bacteria.

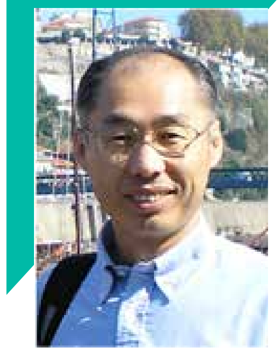
These facts remind us that marine bacterial communities possess novel or unknown antibiotic-resistance genes of marine origin. If the marine-origin resistance genes are accompanied by mobile genetic elements, these might invade the human environment via aquaculture products or workers.
The resistance genes movement between food animals and farmers is known, with common enteric bacteria present in both.

On the other hand, it is known that the bacterial flora in human and fish/seawater are quite different. However, distribution of common transferable resistance genes in marine bacteria and human bacteria suggests that humans and marine environment are interlinked. Some pathogens are common in fish and humans (Heuer et al., 2009). This should be the basis of the "One Health" concept, that is, human-animal-environment are linked even in the marine environment.

We have published strategies to reduce resistance gene-inflow to the environment (Pruden et al., 2013). In addition to that, we should pay attention to the opposite gene-flow route from the sea to human and animal environments. We can propose suspected gene-flow routes as shown in Fig. 1 with a focus on aquaculture activity.

The marine environment is usually an oligotrophic condition for the bacteria associated to fish or human body. The conjugative horizontal gene transfer is suppressed in oligotrophic condition; however, addition of organic matters restored the conjugative gene transfer (Goodman et al., 1993; Kohyama and Suzuki, 2019). Artificial food is spread into aquaculture site and the fish defecate, giving much organic matters to the environment. Aquaculture environment plays a role, not only a reservoir of antibiotic-resistance genes, but also at the stage of horizontal gene transfer, if conditions are appropriate.

In order to produce healthy and safe aquaculture products, control of feeding amount and prevention of pollution in fishing grounds are essentially needed as well as appropriate administration of antibiotics. These strategies decrease diseases in fish, and then leads to reduction in the use of antibiotic.



Satoru Suzuki, PhD. Professor of Microbiology, Center for Marine Environmental Studies, Ehime University, Matsuyama, Japan
1980 B.Sc. in Hokkaido University, Hakodate, Japan, in Food Science
1985 PhD. in Hokkaido University, Sapporo, Japan, in Pharmaceutical Science
1985-1987 Postdoc in University of Alberta, Edmonton, Canada
1987-1992 Assistant Professor in Hokkaido University, Hakodate, Japan
1992-2000 Associate Professor in Kochi University, Nankoku, Japan
2000-Present position Associate editor: Frontiers in Microbiology, Microbes and Environments
Present research interest: Antibiotic resistance in aquatic environments

References

Abe, K., Nomura, N. and Suzuki, S. (2020) Biofilms: Hot spots of horizontal gene transfer (HGT) in aquatic environments, with focusing on a new HGT mechanism. FEMS Microbiol. Ecol., https://doi.org/10.1093/femsec/fiaa031

Antunes, P., Camps, J., Mourão, J., Pereira, J., Novais, C. and Peixe, L. (2018) Inflow water is a major source of trout farming contamination with Salmonella and multidrug resistant bacteria. Sci. Total Environ., 642, 1163-1171.

Aoki, T., Egusa, S., Ogata, Y. and Watanabe, T. (1971) Detection of resistance factors in fish pathogen Aeromonas liquefaciens. J. Gen. Microbiol., 65, 343-349.

Balcázar, J.L., Subirats, J. and Borrego, C.M. (2015) The role of biofilms as environmental reservoirs of antibiotic resistance. Front. Microbiol., 6, 1216, doi:10.3389/fmicb.2015.01216

Cebello, F.C., Godfrey, H.P., Tomova, A., Ivanova, L., Dülz, H., Millanao, A. and Buschmann, A.H. (2013) Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. Environ. Microbiol., 15, 1917-1942.

Fricke, W.F., Welch, T.J., McDermott, P.F., Mammel, M.K., LeClerc, J.E., White, D.G., Cebula, T.A. and Ravel, J. (2009) Comparative genomics of the IncA/C multidrug resistance plasmid family. J. Bacteriol., 191, 4750-4757.

Gebreyes, W., Wittum, T., Habing, G., Alali, W., Usui, M. and Suzuki, S. (2017) Chapter 4. Spread of antibiotic resistance in food animal production systems. in Foodborne Diseases, third edition. Elsevier, 105-130, ISBN:978-0-12-385007-2.

Goodman, A.E., Hild, E., Marshall, K.C. and Hermansson, M. (1993) Conjugative plasmid transfer between bacteria under simulated marine oligotrophic conditions. Appl. Environ. Microbiol., 59, 1035-1040.

Heuer, O.E., Kruse, H., Collignon, G.C., Karunasagar, I. and Angulo, F.J. (2009) Human health consequences of use of antimicrobial agents in aquaculture. Clin. Inf. Dis., 49, 1248-1253.

Klase, G., Le, S., Kim, J., Zo, Y-G. and Lee, J. (2019) The microbiome and antibiotic resistance in integrated fishfarm water: Implications of environmental public health. Sci. Total Environ., 649, 1491-1501.

Kohyama, Y. and Suzuki, S. (2019) Conjugative gene transfer between nourished and starved cells of Photobacterium damselae ssp. damselae and Escherichia coli. Microbes Environ., 34, 388-392.

Muziasari, W.I., Pitkänen, L.K., Sørum, H., Stedtfeld, R.D., Tiedje, J.M. and Virta, M. (2017) The resistome of farmed fish feces contributes to the enrichment of antibiotic resistance genes in sediments below Baltic Sea fish farms. Front. Microbiol., 7, 2137, doi: 10.3389/fmicb.2016.02137

Pruden, A., Larsson, D.G.J., Amézquita, A., Collignon, P., Brandt, K.K., Graham, D.W., Lazorchak, J.M., Suzuki, S., Silly, P., Snape, J.R., Topp, E., Zhang, T. and Zhu, Y-G. (2013) Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ. Health Perspect., 121, 878-885.

Razavi, M., Marathe, N.P., Gillings, M.R., Flach, C-F., Kristiansson, E. and Larsson, D.G.J. (2017) Discovery of the fourth mobile sulfonamide resistance gene. Microbiome, 5, 160, DOI 10.1186/s40168-017-0379-y

Suzuki, S. and Hoa, P.T.P (2012) Distribution of quinolones, sulfonamides, tetracyclines in aquatic environment and antibiotic resistance in Indochina. Front. Microbiol., 3, 67, doi: 10.3389/fmicb.2012.00067

Suzuki, S., Ogo, M., Miller, T.W., Shimizu, A., Takada, H. and Siringan, M.A. (2013) Who possesses drug resistance genes in the aquatic environment? : sulfamethoxazole (SMX) resistance genes among the bacterial community in water environment of Metro-Manila, Philippines. Front. Microbiol., 4, 102, doi:10.3389/fmicb.2013.00102

Suzuki, S., Nakanishi, S., Tamminen, M., Yokokawa, T., Sato-Takabe, Y., Ohta, K., Chou, H-Y., Muziasari, W.I. and Virta, M. (2019) Occurrence of sul and tet(M) genes in bacterial community in Japanese marine aquaculture environment throughout the year: profile comparison with Taiwanese and Finnish aquaculture waters. Sci. Total Environ.,699, 649-656.

Tamminen, M., Karkman, A., Lohmus, A., Muziasari, W., Takasu, H., Wada, S., Suzuki, S. and Virta, M. (2011) Tetracycline resistance genes persist at aquaculture farms in the absence of selection pressure. Environ. Sci. Technol., 45, 386-391

THINK-DO-TANK AMR GENEVA INTERNATIONAL

A Research and Implementation Think-Do-Tank on Antimicrobial Resistance AMR

ANTIMICROBIAL RESISTANT FUNGAL INFECTIONS

SECTION III

AMR IN FUNGAL INFECTIONS: AT THE INTERSECTION OF SUSTAINABLE AGRICULTURE AND HUMAN HEALTH THREATS

Abstract

Fungi are major pathogens of humans, animals, and plants. Controlling fungal pathogens is of major importance for both human health and food security. There are very few antifungal agents available, and the same ones are frequently used in both human health and agriculture, which has led to the rapid emergence of resistant fungal pathogens. In this article we consider the role of agricultural chemical use and misuse in driving drug resistance in human pathogens, taking the emergence of azole-resistant *Aspergillus* in the rice-farming Mekong region of Vietnam as an example.

"

The threat of so few fungicide modes of action is that when a fungal disease develops resistance to one fungicide, all other fungicides which share the same mode of action [...] are also at risk.

Centre for Crop and Disease Management, Department of Environment & Agriculture, Curtin University, 2017

"

Dr Justin Beardsley Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Australia

Prof David Guest, Sydney Institute of Agriculture, University of Australia

FUNGI ARE IMPORTANT HUMAN PATHOGENS, AND RESISTANCE IS AN EMERGING PROBLEM

The principal ecological role of fungi is decomposing the planet's organic waste and freeing nutrients into the environment to be utilised by other organisms. Fungi have always coexisted with other organisms and are also increasingly recognized as an important component of our own internal environment, with the right mix of fungi in a 'mycobiome' playing a role in gut and skin health. A few are pathogens, causing disease of humans, animals and plants. As animals, our closest evolutionary relatives are fungi, with whom genetics are far more similar than we are with plants, bacteria or viruses.

As pathogens, fungi are described as 'hidden killers'. They have the capacity to emerge rapidly and bring about extinction level events, as demonstrated by chytrid infection of amphibians[2] which emerged from the Korean peninsula within the last century and devastated global frog populations.

In plants, fungal diseases such as Fusarium wilt of bananas, stem rust of wheat, and blast of rice have the capacity to destroy staple crops and seriously undermine food security[3]. Humans are not exempt – indeed, fungal diseases are amongst the biggest threats to human health. They cause over 1.6 million deaths annually (similar to the number of tuberculosis deaths, and over 3 times the deaths from malaria)[4], most frequently striking people with existing health problems, such as cancer, chronic lung disease, tuberculosis, HIV, diabetes, or those taking immune-suppressants including steroids. Many of these invasive, high mortality diseases[4] are caused by the fungal pathogens *Candida spp* and *Aspergillus spp*.

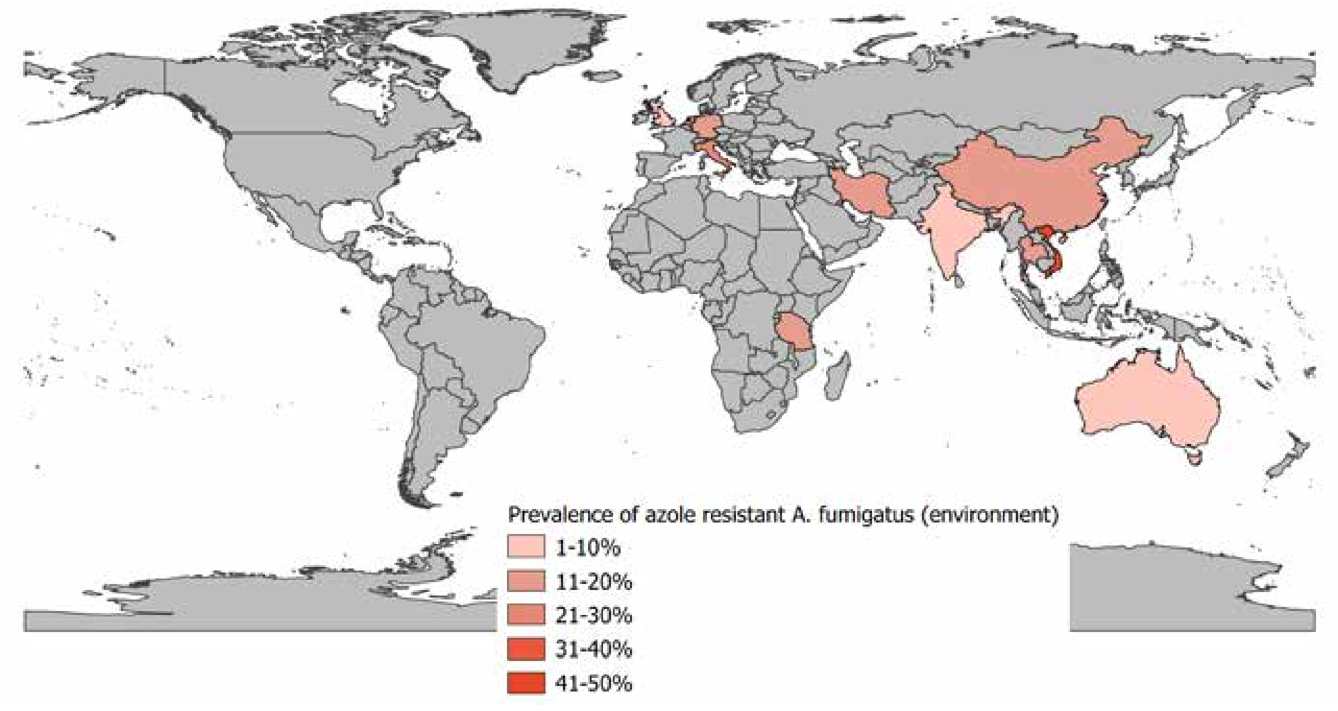
The genetic similarity between humans and fungi make it very difficult to develop effective and safe antimicrobials for fungal infections, since what is toxic to one is often also toxic to the other. As a result, the anti-fungal armamentarium is small, with only four classes of drugs that target fungi available for use in human and animal medicine and plant disease management. However, the very reason fungi have so successfully evolved and adapted to diverse and changing environments, their unusually flexible genetics, also enables them to rapidly overcome these drugs. The lack of options makes the emergence of 'superbugs' from the fungal world especially alarming.

There have been numerous reports illustrating the rapid emergence of intractable fungal pathogens. Most recently, *Candida auris* caused global panic. This previously unknown yeast, from the group of fungi that causes thrush, was first grown from an ear swab taken from a patient in Japan in 2009.

In the decade since, it has appeared on five continents, causing often-fatal infections in critically ill patients[4]. It can be resistant to all four major classes of anti-fungal drug, making treatment difficult, and is so tenacious that contaminated hospitals have had to close down to get rid of it. Although it tends not to infect healthy people, those who are sick for other reasons, or require surgery, are at risk. So much so that the American Centre for Disease Control and Prevention (CDC), the European Centre for Disease Control (ECDC) and Public Health England (PHE) have all issued public health alerts.

Another largely ignored fungus, *Aspergillus fumigatus*, has also gained notoriety over the past ten years. This organism thrives in warm dark places where it decomposes organic matter, such as in compost heaps. However, its spores, once inhaled, proliferate inside our bodies under the right conditions (such as weakened immunity, or lungs damaged by disease, smoking, or pollution). This leads to disease ranging from isolated fungal balls through to invasive disease with case fatality rates up to 70%[4].

A. fumigatus has historically been susceptible to a class of anti-fungals called azoles. These drugs, which target the fungal cell-membrane, are cheap, potent, and non-toxic and are one of the main medical, as well as agricultural, weapons against fungi[5]. However, the utility of these vital drugs in treating *Aspergillus* is threatened by the development of antimicrobial resistance (AMR). For the majority of patients globally, azoles are the only avail-



able therapy, and resistance leads to worse clinical outcomes[6]. Unlike *Candida auris*, we understand what is driving the emergence of resistant *A. fumigatus*: the widespread use of azoles in agriculture.

AGRICULTURAL PRACTISES HAVE AN IMPACT ON HUMAN PATHOGENS

Azoles are not only relied upon by doctors to treat patients, but by farmers who need to protect their crops and livestock. Azoles are amongst the most highly used pesticides globally, from the tulip growers of the Netherlands to rice farmers of the Mekong, and have become vital to food security.
The role of agricultural azoles causing resistant *Aspergillus* infections in humans was first raised in 2009 by researchers in the Netherlands[7] where approximately 12% of environmental *A. fumigatus* isolates were found to be resistant, likely driven by high azole usage in the tulip industry.

Subsequently, researchers in several other countries have discovered rates of resistance typically between 10-25% (and higher in intensive azole use areas e.g. 33% in an Indian tea-garden). Our soon to be published data show average resistance rates across a range environmental niches in the Mekong region of Vietnam at unprecedented levels of 50%.

In Vietnam, farmers use azoles heavily in rice, fruit, and shrimp farming. Azoles are amongst the top selling pesticides in the country[8]. The use of agricultural chemicals is poorly regulated in Vietnam where farmers apply their anti-fungals without adequate disease diagnostic or technical advice and no knowledge of the mode of action, leading to widespread inappropriate use of the chemicals. This uninformed and indiscriminate deployment of azoles appears to be pushing *Aspergillus* to develop resistance.

Our data show high rates of resistance in areas azoles are used intensively (such as rice farms), and low rates in uncontaminated wetland regions. Vietnam does not conduct any surveillance for resistance in clinical isolates of *Aspergillus*, but it is well-established that strains that cause infection in people originate from their environments. The risk for the farmers of the Mekong is that despite never having taken anti-fungal drugs, they will present with infections already resistant to azoles.
The remaining drug choices are toxic, expensive, and often need to be given intravenously. For this particular population, many of whom have recovered from tuberculosis and are thus at risk from *Aspergillus* infection, alternative treatments are practically unavailable.

BALANCING FOOD SECURITY AND HUMAN HEALTH

While the use of antibacterials in agriculture is restricted because the risks of AMR in human pathogens are recognised in research and by major research funders, AMR in fungal pathogens is frequently neglected[1]. The use of near identical agents to control disease in agriculture and healthcare calls for a multi-disciplinary response that can address the whole One Health triad at the same time. This One Health approach, thus far, has also been lacking. Anti-fungals in general, and azoles in particular, contribute significantly to food security. Growing global populations make increasing demands on the agricultural sector, with loss of plants, harvests, or animals becoming increasingly unaffordable[9,10].

In this setting, agricultural azole use will expand, adding further selective pressure on to human pathogens. This effect is likely to be especially acute in areas such as the Mekong Delta where regulation of agrichemicals is weak, profit margins are slight, and the land is farmed intensively. It is critical that our food security needs are carefully balanced against the health risks of anti-fungal AMR in important human pathogens.

Given the very high burden of disease caused by fungi and our limited anti-fungal armamentarium, urgent attention must be given to the development of new and distinctive classes of anti-fungals for agricultural and medical use. We must conduct more surveillance for resistance, especially in areas such as the Mekong Delta.

We need to make sure we are stewarding our resources in the best possible way, by ensuring that agricultural azoles are being used only as required, and that regulations on use are enforced. Achieving this balance will require a co-ordinated One Health approach and considerable government and industry commitment.

Dr Justin Beardsley, Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Australia. is an infectious disease physician and clinical researcher focussed on fungal infections. He was previously based in Ho Chi Minh City at the Oxford University Clinical Research Unit, where he developed a research programme investigating cryptococcal meningitis, and examining the role of *Aspergillus* infection in long-term tuberculosis mortality. During this work he identified unprecedented levels of anti-fungal drug resistance in environmental isolates of *Aspergillus*, which threatens to undermine international treatment guidelines.

Prof David Guest, Sydney Institute of Agriculture, University of Australia is a professor of Plant Pathology and Development Agriculture. He has worked with farmers extensively throughout Southeast Asia and the Pacific region, and as a result has a deep understanding of agricultural practises and food security in the region. He is committed to OneHealth research, and currently leads a major project in Papua New Guinea which aims to improve the livelihoods of cocoa farmers by investigating the constraints on their productivity through a One Health prism.

References

(1) Brown, G. D. et al. Hidden killers: human fungal infections. Sci Transl Med 4, 165rv13 (2012).

(2) O'Hanlon, S. J. et al. Recent Asian origin of chytrid fungi causing global amphibian declines. Science. 360, 621–627 (2018). DOI: 10.1126/science.aar1965

(3) Fisher, M. C., Gow, N. A. R. & Gurr, S. J. Tackling emerging fungal threats to animal health, food security and ecosystem resilience. Philos. Trans. R. Soc. B Biol. Sci. 371, (2016).

(4) Bongomin, F., Gago, S., Oladele, R. & Denning, D., Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision. J. Fungi 3, 57 (2017).

(5) Maertens, J. A. History of the development of azole derivatives. Clin. Microbiol. Infect. Suppl. 10, 1–10 (2004).

(6) Pfaller, M. A. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. Am J Med 125, S3-13 (2012).

(7) Snelders, E. et al. Possible Environmental Origin of Resistance of *Aspergillus fumigatus* to Medical Triazoles. Appl. Environ. Microbiol. 75, 4053–4057 (2009).

(8) Vietnamese Pesticide Assocation. Agriculture in Vietnam and Status of Pesticide Market. (2015). Available at: http://cacasiasummit.com/Uploads/Download/7-Vietnam Agricuture and Status of Pesticides Market.pdf.

(9) Brauer, V. S. et al. Antifungal agents in agriculture: Friends and foes of public health. Biomolecules 9, 1–21 (2019).

(10) Hof, H. Critical annotations to the use of azole antifungals for plant protection. Antimicrob. Agents Chemother. 45, 2987–90 (2001).

COVID-19 & AMR
THE NEGLECTED KEY IS:
INFECTION PREVENTION & CONTROL
INCLUDING FOR AIRBORNE DISEASE

SECTION IV

FROM SARS TO MERS TO COVID-19
UNCOVERING NEEDS
IN INFECTION PREVENTION AND CONTROL,

BROADENING THE RESPONSE AND BUILDING PROGRAMMES BASED ON WHO CORE COMPONENTS

Abstract

In this article, we review how outbreaks of respiratory disease associated with coronaviruses (including SARS, MERS, and SARS-COV-2) led to realizations for the need of Infection Prevention and Control (IPC) Programmes. We describe the status of IPC programmes in the WHO Eastern Mediterranean Region (EMR), the critical role of IPC programmes for global, regional, and national preparedness and response to emerging threats. We finally highlight the WHO IPC response in the region and outline a way forward to build on this opportunity to implement future strong IPC programmes.

> ***"In both high and low resource settings, the pandemic disrupted supply chains and depleted stocks, including medical supplies, IPC supplies, and equipment. These shortages could have potentially devastating consequences on the management of multidrug-resistant TB. Despite the initial dramatic situations, the COVID-19 pandemic led to positive development in the field of IPC. WHO, Africa CDC, and other international partner are working on a model public health law and legal framework that will guide and underpin the operations of IPC within LMIC."***

Maha Talaat, Regional Adviser for Antimicrobial Resistance and Infection Prevention and Control, Eastern Mediterranean Regional Office, World Health Organization, Cairo, Egypt
Bassem Zayed, Technical Officer, EMRO, WHO,
Yvan Hutin, Director of the department of Universal Health Coverage, Communicable Diseases, EMRO, World Health Organization

PROGRESS IN IPC WERE ALWAYS ROOTED IN EMERGING CHALLENGES

IPC is a discipline and a scientific approach to prevent harm caused by infections to patients and health workers. While health systems have an ethical duty to "do not harm" when patients receive medical care, IPC has never been a natural function of health systems like other preventive and curative interventions. Most progress in IPC resulted from lessons learned the hard way In Vienna in 1847, Ignaz Semmelweis struggled to get his contemporaries to understand that the failure to wash hands was the cause of septicaemia in women who had just delivered[1]. While global infectious disease epidemics and pandemics pose a major risk to global health security and socio-economic stability, they also advanced IPC. In the late 1980s, the concern that HIV could be spread through microscopic quantities of blood in health care setting or in the community led to the concept of universal precautions[2]. The concept of universal precautions referred to the idea that anyone could be potentially infected with HIV and that a set of precautions had to be applied universally, to everyone, and in all settings, including in the community. Universal precautions then expanded in scope to lead to the concept of standard precautions[3], a baseline set of measures to prevent the transmission of pathogens for everyone in health care setting. At the end of the 20th century, IPC improved in high income countries.
In lower and middle income (LMIC) countries, initiatives for IPC started later and usually, with a more restricted scope. In 1999, WHO launched the safe injection global network to address transmission of bloodborne pathogens through unsafe injections[4]. In 2005, WHO launched a hand hygiene initiative[5], including guidelines[6] and campaigns[7].

IPC has now become particularly urgent in LMIC countries given the expansion of universal health coverage. Since the 2000, several outbreaks and epidemics were amplified in the health sector (e.g., SARS, pandemic influenza H1N1, MERS-CoV). These were wake-up calls to political and public health leaders around the world[8,9]. The international health regulations (IHR) made explicit reference to IPC, but implementation in LMIC remained limited. In 2014, the outbreak of Ebola in West Africa was the strongest warning. It pointed to the implications of a possible failure to contain transmission, not only in the community in Africa but also in health care setting of high-income countries where the virus was introduced[10,11]. From 2015, the Sustainable Development Goals (SDG) provided another framework to underline the importance of IPC as a strong contributor to the achievement of the health-related UN's SDG including quality universal health coverage.

IPC being a cross-cutting discipline, it also helps effective implementation of major global health priorities, including the IHR, antimicrobial resistance (AMR), patient and health worker safety, and integrated people-centered care. At the beginning of the 2000s, intense use of antimicrobial agents and their spread in health care settings and communities led to the emergence of more multidrug resistant pathogens. This drew the attention to the importance of strengthening the culture of IPC and implementing effective IPC programmes to reduce the prevalence and spread of resistant infections in hospitals. In 2015, WHO developed a broader guidance on IPC with the core components that addressed the need to invest in real IPC improvements through IPC capacity building, continuous resources and dedicated funding[12]. While there was a progressive increase in awareness and more technical guidance available, few LMICs made substantial progress towards establishing comprehensive IPC programmes.

HOW SARS-COV-2 DIFFERED FROM THE PREVIOUS RESPIRATORY VIRUSES' OUTBREAKS?

SARS and the Middle East respiratory syndrome coronavirus (MERS-CoV)

The SARS epidemic in 2003 provided lessons for the importance of good infection control measures in the prevention of nosocomial infections. It was characterized by super spreading events, which accounted for 71% of SARS cases in Hong Kong and Singapore.

The MERS-CoV in 2013 was effectively transmitted within healthcare facilities, where major breakdown in IPC procedures had occurred. It caused multiple large healthcare-associated infections and outbreaks, where infections among healthcare workers ranged from 18% in South Korea to 31% in the Kingdom of Saudi Arabia[13,15]. The emergence of these pathogens showed how limited or non-existent IPC programmes, combined with an inadequate water supply, poor sanitation, and a weak hygiene infrastructure in health facilities could threaten global health security and how health facilities could become locations for outbreak amplification among staff and patients and transmission back to the community. SARS and MERS-CoV were highly lethal (high case fatality ratio) and a high proportion of case patients were healthcare workers. However, the transmissibility outside of health care facilities was relatively low. This allowed a more focus control that lead to containment. The threat of MERS-CoV in the middle East helped building better IPC in health care facilities in Gulf countries including the Kingdom of Saudi Arabia.

COVID-19

In 2019, the emergence of a respiratory illness linked to a novel coronavirus (SARS-COV-2) represented a test of the global capacity to detect and manage emerging disease threats. COVID-19 was less lethal (lower-case fatality ratio) but its transmissibility outside of health care facilities was higher. As a result, health care workers account for a lower proportion of case-patients ranging from 7% in the EMR up to 14% primarily from European and American countries, where transmission of infections was contributed mainly to community rather than healthcare.

This made it more difficult to control, prevent and contain. Widespread transmission outside of health care facilities led to the emergence of the need to implement IPC at the community level. Communities acceptance of these new measures varied around the world, with a few public debates around various effective measure like mask use.

WHO RESOURCES, INCLUDING IPC GUIDELINES:

In November 2016, WHO published guidelines on core components of infection prevention and control programmes at the national and acute health care facility levels. These were the first international evidence-based guidelines. They established a foundation for WHO strategies to prevent current and future threats from emerging infectious diseases[16]. The guidelines defined a set of important IPC core components (6 at national and 8 at facility level) to help plan, organize and implement an effective IPC programme. These core components and their elements, should be implemented in line with the priorities of the IPC programme and resources available, and adapted to both national and healthcare facility levels. Along with the guidelines, WHO also published toolkits for implementation of the core components[17] and guidelines on minimum IPC requirements[18]. These can facilitate the stepwise implementation of the WHO core components, where IPC is limited or non-existent. Minimum IPC requirements are standards that should be in place at both national and health facility levels to provide minimum protection and safety to patients, healthcare workers, and visitors.
Today, WHO aims at achieving the IPC minimum requirements everywhere while developing more robust and comprehensive IPC programmes where possible.

THE SITUATION OF IPC IN EMR AT THE TIME THAT COVID STRUCK

In 2019, EMRO surveyed the region to assess the national IPC programmes using the WHO IPCAT2 tool[19]. The main purpose of the IPCAT2 tool is to identify strengths and weaknesses to plan for improvement and develop targeted annual IPC action plans. The tool assesses the six main core components of IPC and provides a score for each of the components. Data were collected through personal interviews with the national IPC leads or their representatives.

The capacities of IPC within countries in the EMR was limited. Only 13 out of 22 (60%) of countries had the national appropriate IPC governance. Nine countries (41%) had developed national IPC guidelines within the last 5 years, 7 (31.8%) countries had active IPC education programmes, and 6 countries (27.3%) had either multimodal strategies or national IPC monitoring plans. IPC programmes were stronger in high income countries and in countries that had stronger health systems (Figure 1).

The region continues to score low on several indicators, including unsafe health care injections[20]. Major challenges in several countries, leading to transmission of resistant pathogens such as XDR typhoid[21], and outbreaks of HIV in health care setting[22].

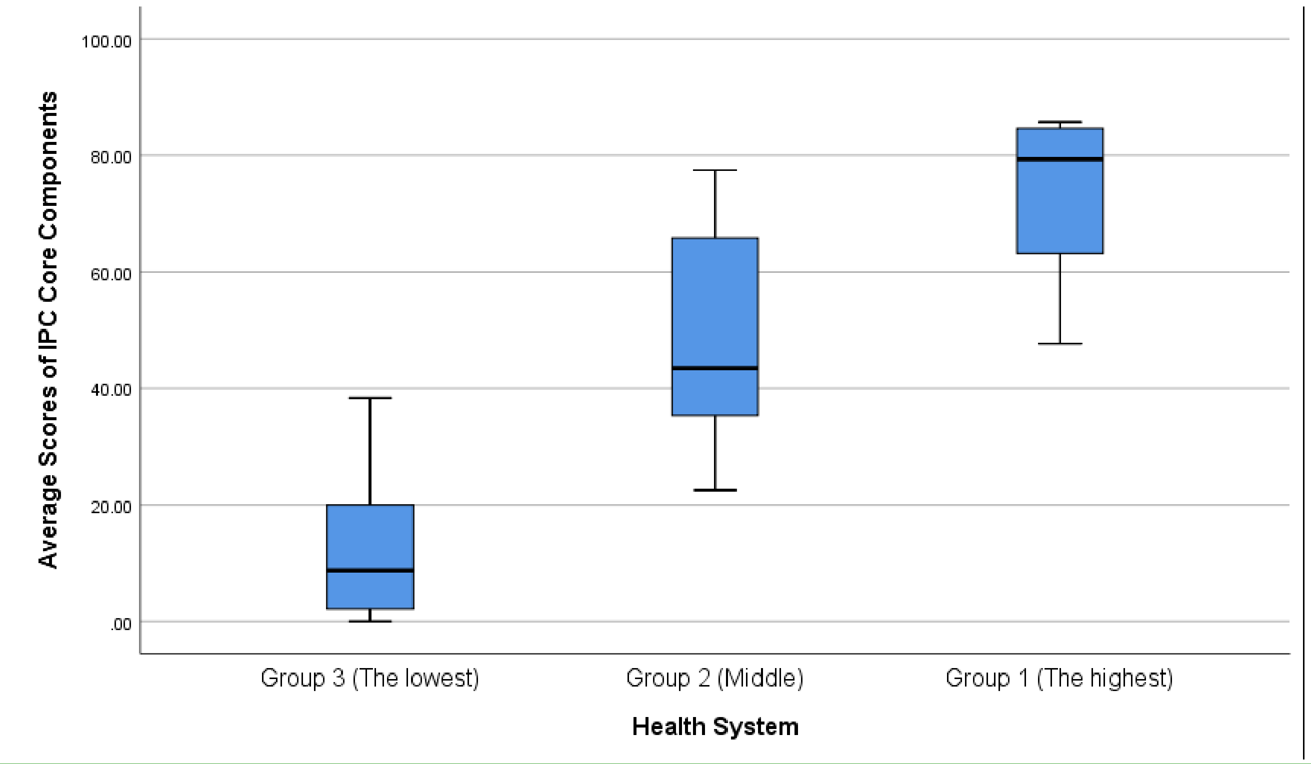


Figure 1: Average IPC core components scores by health system classification score in countries of the Eastern Mediterranean Region, 2019

WHO EMRO RESPONSE TO THE IPC CHALLENGES DURING COVID-19

Coordination

Even before a first case of COVID-19 was reported in EMR, in January 2020, the WHO regional office established an incident management support team (IMST) to coordinate and steer the response to COVID-19 by bringing together regional partners. It consists of eight pillars or workstreams. IPC was one of the sub-pillars under the health operations and technical expertise. The IPC team in the IMST led the response in 22 countries of the region where they disseminated up-to-date WHO IPC guidance, reviewed national IPC documents, and provided continuous IPC training courses to raise the capacities of hospital IPC teams and staff engaged in clinical care[23].

Country support

Throughout the response, we have seen dramatic improvements in the IPC capacities over the short time to provide an immediate response. Examples include countries that assessed their IPC capacities, assigned national IPC groups to coordinate the response, updated WHO IPC guidance to reflect their context and capacities, provided intensive IPC training to frontline health workers, and ensured availability of needed IPC supplies. These country efforts constitute important first steps that need to be followed by further efforts to institutionalize IPC and strengthen health systems in the future.

IPC supply chain management during COVID-19:

In both high and low resource settings, the pandemic disrupted supply chains and depleted stocks, including medical supplies, IPC supplies, and equipment. This catapulted the eighth core component of IPC (built environment, materials, and equipment for IPC) to the headlines in the popular press and social media. Purchases made in the context of panic and irrational use of PPE depleted supplies of N95 respirators. These shortages could have potentially devastating consequences on the management of multidrug-resistant TB in LMIC.

Governments should give clear guidance on the use of PPE and act promptly to secure adequate supplies and stocks of essential PPE to prevent shortages in the context of the COVID-19 response. Regional production of medical supplies on all continents may reduce the risks of shortages of PPE at crucial times.

BUILDING ON THE MOMENTUM CREATED BY COVID-19

Despite the initial dramatic situations, the COVID-19 pandemic led to positive development in the field of IPC. Several countries in the region took important initial steps towards establishing and sustaining IPC programmes. In May 2020, Pakistan published its first national IPC guidelines[25]. In October 2020, Afghanistan formulated a request for assistance to WHO to build a sustainable IPC programme. Iraq updated their national IPC governance mechanisms to ensure effective future implementation of IPC. We now need to respond to the demand that was created. Implementation of IPC against COVID-19 represents a lasting contribution to prevent the spread of AMR infections now and for the coming years. We urge countries to take decisive and visible political commitment, including IPC policy development and enforcement, fostering and promoting IPC as a quality indicator, and ensuring availability of both human and infrastructure resources. Countries should develop comprehensive strong legal foundations for IPC to promote safe health care services, patient safety and quality universal health coverage that are relevant to health workers and patients at every single health-care encounter.

WHO, Africa CDC, and other international partners are working on a model public health law and legal framework that will guide and underpin the operations of IPC within LMIC.

This will capture the key pieces that were missing in the puzzle so far, including accountability mechanisms, resources requirements, leadership structure, monitoring and evaluation framework. Success in this field would be a substantial contribution to WHO's three billions and the sustainable development goals as strong health systems that include solid IPC programmes are the best defense to prevent outbreaks from becoming epidemics.

Dr. Maha Talaat is the regional adviser for antimicrobial resistance and infection prevention and control at the Eastern Mediterranean Regional Office, World Health Organization. She leads a multidisciplinary program to enhance the capacities of 22 countries in the region to combat AMR and strengthen IPC programs. Dr. Talaat holds master's and doctoral degrees in public health and epidemiology and has more than 50 publications in international journals and presented in 53 international meetings and conferences. She has more than 30 years of experience in public health and epidemiology of emerging infectious diseases. She has been leading more than 30 national and international public health programs in various technical areas such as supporting countries in surveillance, IPC, and AMR.

Dr. Bassem Zayed has more than 15 years of experience in the field of Infection Prevention & Control (IPC) and antimicrobial resistance (AMR) and is currently working in the AMR/IPC Unit in the WHO Eastern Mediterranean Regional Office. His research and work interests include development and implementation of national action plans on AMR & IPC, interventions and surveillance of antimicrobial resistance and healthcare associated infection (HAI), Antimicrobial consumption, use & stewardship programs, implementation of WHO core components of national and facility levels IPC programs, and prevention of surgical site infections.

Dr Yvan J-F. Hutin is the director of the Department of Universal Health Coverage, Communicable Diseases (UHC-DCD) at the WHO Regional Office for the Eastern Mediterranean Region. Following his MD an a specialization in hepato-gastroenterology in Paris, France and an MSc in clinical tropical medicine at the London School of Tropical Medicine and Hygiene, he joined the Epidemic Intelligence Service of the United States Centers for Disease Control and prevention and completed a PhD at the Swiss Tropical Institute, in Basel. As part of his international public health experience, he worked in Burkina Faso (including work on Guinea worm), in Uganda (including work on sleeping sickness) and in Sweden at the European Centre for Disease Control. During his WHO career, he initiated the Safe Injection Global Network project (SIGN) at WHO headquarters, assisted India in the setup of its Field Epidemiology Training Programme (FETP), was the international co-manager of the GAVI China project on hepatitis B vaccine introduction and injection safety and coordinated strategic information at the Global Hepatitis Programme of WHO headquarters. His areas of expertise include epidemiology, prevention, care and treatment of viral hepatitis, public health training, economic analyses and financing. Dr Hutin co-authored more than 120 publications in peer review journals.

References

(1) Cavaillon JM, Chrétien F. From septicemia to sepsis 3.0 - from Ignaz Semmelweis to Louis Pasteur. Microbes Infect. 2019 Jun-Jul;21(5-6):213-221. doi: 10.1016/j.micinf.2019.06.005. Epub 2019 Jun 27. PMID: 31255674

(2) CDC. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep 1988;37(24):377-82, 87-8

(3) Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1996;17(1):53-80.(s)

(4) Hutin YF and Chen RT. Injection safety: a global challenge. Bulletin of the World Health Organization, 1999, 77 (10)

(5) World Alliance for Patient Safety. The Global Patient Safety Challenge 2005–2006 "Clean Care is Safer Care". Geneva, World Health Organization, 2005

(6) WHO Guidelines on Hand Hygiene in Health Care. Geneva: World Health Organization; 2009, https://www.who.int/publications/i/item/9789241597906, accessed online on 23 Nov 2020

(7) World Health Organization. 'My 5 moments for hand hygiene'. 2009, http://www.who.int/infection-prevention/campaigns/cleanhands/5moments/en/, accessed 23 Nov 2020

(8) Allegranzi, B., Kilpatrick, C., Storr, J., Kelley, E., Park, B. J., & Donaldson, L. (2017). Global infection prevention and control priorities 2018–22: a call for action. The Lancet Global Health, 5(12), e1178-e1180

(9) Zingg, W., Storr, J., Park, B. J., Ahmad, R., Tarrant, C., Castro-Sanchez, E., ... & Pittet, D. (2019). Implementation research for the prevention of antimicrobial resistance and healthcare-associated infections; 2017 Geneva infection prevention and control (IPC)-think tank (part 1). Antimicrobial Resistance & Infection Control, 8(1), 87.

(10) Lópaz, M. A., Amela, C., Ordobas, M., Domínguez-Berjón, M. F., Álvarez, C., Martínez, M., ... & Astray, J. (2015). First secondary case of Ebola outside Africa: epidemiological characteristics and contact monitoring, Spain, September to November 2014. Eurosurveillance, 20(1), 21003.

(11) Chevalier, M. S., Chung, W., Smith, J., Weil, L. M., Hughes, S. M., Joyner, S. N., ... & Threadgill, H. (2014). Ebola virus disease cluster in the United States—Dallas county, Texas, 2014. MMWR. Morbidity and mortality weekly report, 63(46), 1087.

(12) Storr, J., Twyman, A., Zingg, W., Damani, N., Kilpatrick, C., Reilly, J., ... & Allegranzi, B. (2017). Core components for effective infection prevention and control programmes: new WHO evidence-based recommendations. Antimicrobial Resistance & Infection Control, 6(1), 6.

(13) Assiri, A., McGeer, A., Perl, T. M., Price, C. S., Al Rabeeah, A. A., Cummings, D. A., ... & Madani, H. (2013). Hospital outbreak of Middle East respiratory syndrome coronavirus. New England Journal of Medicine, 369(5), 407-416.

(14) Kim, K. H., Tandi, T. E., Choi, J. W., Moon, J. M., & Kim, M. S. (2017). Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. Journal of Hospital Infection, 95(2), 207-213.

(15) Al-Tawfiq, J. A., & Memish, Z. A. (2016). Infection control measures for the prevention of MERS coronavirus transmission in healthcare settings.

(16) Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/251730, accessed 23 Nov)

(17) Interim Practical Manual supporting national implementation of the WHO guidelines on core components of infection prevention and control programmes. Geneva: World Health Organization; 2017, http://www.who.int/infection-prevention/tools/core-components/cc-implementation-guideline, pdf, accessed 23 Nov 2020

(18) Minimum requirements for infection prevention and control programmes. Geneva: World Health Organization;2019. (https://apps.who.int/iris/handle/10665/333074, accessed 23 Nov 2020)

(19) World Health Organization. Instructions for the national infection prevention and control assessment tool 2 (IPCAT2). No. WHO/HIS/SDS/2017.13. Geneva. World Health Organization, 2017

(20) Hayashi, T., Hutin, Y. J. F., Bulterys, M., Altaf, A., & Allegranzi, B. (2019). Injection practices in 2011–2015: a review using data from the demographic and health surveys (DHS). BMC health services research, 19(1), 600.

(21) Akram, J., Khan, A. S., Khan, H. A., Gilani, S. A., Akram, S. J., Ahmad, F. J., & Mehboob, R. (2020). Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management. BioMed Research International, 2020.

(22) Zaid, M., Ali, M., & Afzal, M. S. (2019). HIV outbreaks in Pakistan. The Lancet HIV, 6(7), e418-e419.

(23) World Health Organization. COVID-19 pandemic response in the Eastern Mediterranean Region, Progress Report of the Incident Management Support Team, January-July 2020. WHO. Regional office for the Eastern Mediterranean Region. WHO-EM/HSEL/002/E.

(24) Hopman, J., Allegranzi, B., & Mehtar, S. (2020). Managing COVID-19 in low-and middle-income countries. Jama, 323(16), 1549-1550.

(25) National guidelines infection prevention and control, Pakistan https://www.nih.org.pk/wp-content/uploads/2020/04/Complete_IPC_Guideliens.pdf, accessed 23 Nov 2020

BUILDING PREPAREDNESS FOR PANDEMICS

Abstract

On July 9th 2020 the World Health Organization (WHO) admitted that COVID-19 is being spread by aerosols as well as by touch and droplets. A letter published by 239 international experts three days before pointed to the incontrovertible evidence of COVID-19 transmission pathways in buildings, and proposed that an effective way to reduce the viral load in spaces was to purge the air in them via open windows. While scientific evidence abounds on the spread of COVID-19 by aerosols in buildings, advice on reducing, or preventing, cross infections between people and spaces indoors is limited, and highlights a glaring flaw in many modern buildings: that their windows cannot be effectively opened. The shift over the last decades away from conditioning buildings with natural ventilation, and radiant heating and cooling systems, towards the use of mechanical circulating pumped air systems for heating, cooling and ventilation exposes building occupants to streams of moving air which has been shown in some cases to be the medium for the transmission of COVID-19 in infected aerosols, with morbidity and mortality impacts.

Indoor Air Quality Standards are now largely written by the Heating, Ventilating and Air-conditioning (HVAC) profession, and their colleagues in an industry which is normally paid according to the amount of equipment it installs in a building. Many national and international regulations, standards and rating schemes require increasing amounts of equipment to be installed in them to meet the rising Standards. The case is made here that a major risk exists to the resilience of our built environment arising from the excessive influence, and proven affiliation bias, of the HVAC profession on standards, policies and policy makers. The paper calls for Big Picture thinking for ways to make the built environment more resilient to the impacts of viral spread by aerosols during epidemics.

Recommendations are made for effective actions for national and city authorities, planners and designers to better protect populations from this and future pandemics.

> *"The shift over the last decades away from natural ventilation, ... towards the use of mechanical circulating pumped air systems for heating, cooling and ventilation exposes building occupants to streams of moving air which has been shown to be the medium for the transmission of COVID-19 in infected aerosols...*
> *Recommendations are made for effective actions*

Susan Roaf, Emeritus Professor of Architectural Engineering, Heriot Watt University, Edinburgh, Scotland, UK

Two hundred thirty-nine scientists from 32 countries signed a letter in the Journal of Clinical Infectious Diseases on the 6th July 2020 saying that COVID-19 is not only spread by touch and droplets sprayed from the mouth and nose but via a third route, aerosols, in which the virus attaches to fine particles floating in the air, and spreads much further[(1)].

The World Health Organization (WHO) conceded three days later that the virus could indeed infect people over far greater distances in lighter aerosol particles. It was forced to admit as much by the growing evidence that aerosols had played a role in COVID-19 outbreaks in restaurants, choirs, buses, cruise ships, meat processing plants, hospitals, call centres, via sewage systems, and in a growing number of other building related examples.

In the face of the strongly worded plea by this group of leading international scientists to change course, a WHO representative claimed that the WHO's panel of thirty-five experts that vets emerging evidence has discussed airborne transmission on at least four occasions, and that the WHO was working with aero-biologists and engineers to discuss emerging evidence and develop better ventilation guidelines[(2)].

So why did this globally influential panel who had known about the aerosol spread of the virus almost since SARS-CoV-2 identification, continue to deny aerosol spread then? Virus spread by aerosols have been previously well proven in robust studies. SARS-CoV-1 spread aerially in 2003 in Hong Kong's Prince of Wales Hospital[(3)], in health care facilities in Toronto and in aircraft. Many other pathogens spread readily as pathogen including Norwalk-like viruses, and Influenza A/H5N1 and tuberculosis, that has been convincingly shown to result in far fewer cross infections in older, spacious hospital wards with high ceilings and large openable windows on more than one wall, than in mechanically ventilated wards[(4)].

The WHO maintained that in the face of the evidence they had adopted a 'precautionary' stance, and steadfastly pushed back against the idea that there is a significant threat of the coronavirus being transmitted by aerosols. The WHO claimed the virus spreads mainly by touching contaminated surfaces and via droplets bigger than aerosols generated by coughing, sneezing and talking.

Droplet particles are >5-$10\,\mu$m in diameter are called respiratory droplets. When they are $<5\,\mu$m in diameter, they are referred to as droplet nuclei and are liable to spread as aerosols. The WHO's main line of proposed defence against COVID-19 was then via spatial distancing, face masks, and hand washing to mitigate against droplet spread, with the use medical masks where high viral loads are.

Many other researchers are increasingly thinking that infection control guidelines should be urgently re-evaluated to account for the predominance of small particle infectious aerosols generated in hospital patients, even in the absence of aerosol-generating procedures. Healthcare facilities are adopting appropriate PPE protective devices for different spaces, shifting from surgical masks to filtering face-piece respirators to powered air-purifying respirators, as necessary in spaces with high aerosol viral loads. They call for the recognition of aerosol transmission of SARS-CoV-2 that could lead to and inform the use of enhanced dilution and directional ventilation, and other environmental control options including air disinfection systems, to reduce and prevent patient and health care worker morbidity and mortality.

The question is WHY did the WHO continue to play down the role of aerosol spread of infections, including SARS-CoV-2? Why do international and national building regulations and standards so often turn a blind eye to this issue?

OPEN THE WINDOWS TO DUMP THE VIRAL LOAD

In the 6th of July letter was a strong plea for the WHO to take seriously the spread of COVID-19 via aerosols with the scientists stressing that an affordable and effective way to reduce aerosol spread is to purge the air containing those aerosols from rooms was by simply opening the windows as shown in Figure 1.

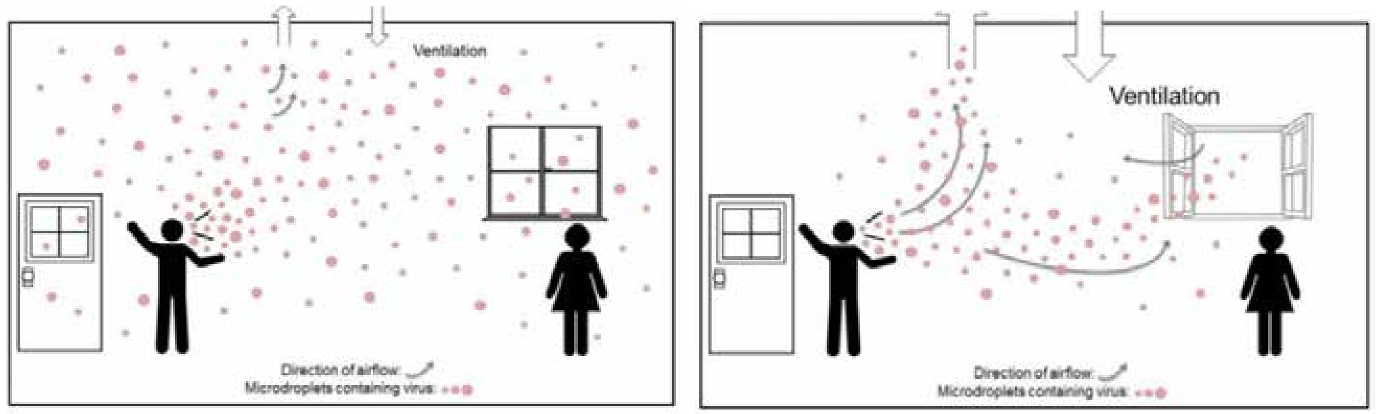


Figure 1. This Figure sent with the COVID letter of the 6th July shows clearly that by opening a window to let the virus escape the amount of it in a rooms can be reduced leading to lower cross-infections risks (Source: 1).

Architects appear to be increasingly realising that simply opening windows may be both beneficial for health reasons and occupant comfort indoors.
In Japan the Architectural profession even recommends opening the windows while keeping the air-conditioning on, even in public buildings like schools in summer(5). Engineers are also beginning to admit that a sensible means of reducing viral load in a space may be to simply open the windows. Politicians like Angela Merkel in Germany are asking everyone to throw open the windows of buildings periodically to reduce the viral load in spaces, especially in homes and schools. That is fine if the windows actually do open.

Building Regulations in the UK, for instance, do not promote the need for opening windows, resulting in many buildings being constructed without them, including hospitals. Architects often appear to have forgotten how to design windows for either ventilation, pollution and infection reduction or to provide the thermal, emotional and sensual delight of a cooling breeze on the skin on a warm day, or the relief of clean, fresh air pouring into a stuffy room derived simply from opening a window(6). The result is a generation that includes many buildings that are simply not Prepared for Pandemics.

HOW IS SARS-COV-2 ACTUALLY SPREAD IN BUILDINGS?

SARS-CoV-2 is released directly into the air, via breathing of COVID-19 patients, as well as by touch and through defecation. The SARS-CoV-2 breath emission rates are affected by many factors, such as disease stage, patient activity, and possibly age, with the highest level of the virus emitted on the breath during the earlier stages of COVID-19 in a patient. Breath emissions of the virus appear not to be steady, but are emitted rather sporadically, which may be related to metabolic activity in the body, changes in environmental conditions around a patient or for other reasons. This Chinese study showed that SARS-CoV-2 can spread by asymptomatic patients, who may not cough or sneeze to generate respiratory droplets, but transmit the virus via the fine aerosol route. Breath samples taken from two patients were positive for coronavirus RNA, but surface swabs from their cell phones, hands, and toilets were negative. Viral RNA was also detected on an air ventilation duct below another patient's bed(7).

It is now well accepted that SARS-CoV-2 can survive for at least three hours in airborne aerosols, and for days on various surfaces, based on a robust laboratory study(8). Studies have detected exhaled virus up to 4m to 8m away from a source patient putting in question the current division of exhaled spread paths into droplets and aerosols(9).

Among the 242 surface swabs quoted in the Chinese study, viral RNA was found most often on toilet bowls (16.7%); floors (12.5%); patient hands, pillowcases, mobile phones, and computer keyboards (4.0%); and surfaces that healthcare staff touched (2.6%). But only two of twenty-two mobile phone surface samples tested positive for viral RNA, and all object handles were negative. Evidence is growing that touch may not be the main route of infection for SARS-CoV-2.
In toilets high viral loads reported indicated that exhaled virus combining with virus aerosolisation from the toilet and sewage systems proved to be major routes of infection during the SARs outbreak of 2003 in Hong Kong(10).

A recent meta-analysis looked at the effectiveness of hygiene interventions in preventing or reducing the spread of illnesses from respiratory viruses showed that hand-washing policies only led to a 16% reduction in acute respiratory across 52 eligible trial studies(11). This, and other studies mentioned here, do not chime with those who claim that surface contacts are likely to be the most significant transmission route.

SARS-COV-2 SPREAD BY AIR-CONDITIONING AND MECHANICAL VENTILATION SYSTEMS

Engineers have claimed that the transmission of the virus depends on both the amount of virus present, and the duration and method of exposure. This only partly explains viral spread in rooms. An early case of the SARS-CoV-2 spread in a windowless restaurant visited the 23rd of January in a restaurant in Guangzhou, China, ten people fell ill after eating lunch in a fifth floor restaurant, infected by the virus in aerosols spread from an air-conditioner. However a key point in this early confirmed example was that those infected by people on the adjacent table were sitting down wind of the air stream from the air-conditioner in the space, some far more than 2m away from the source person(12).

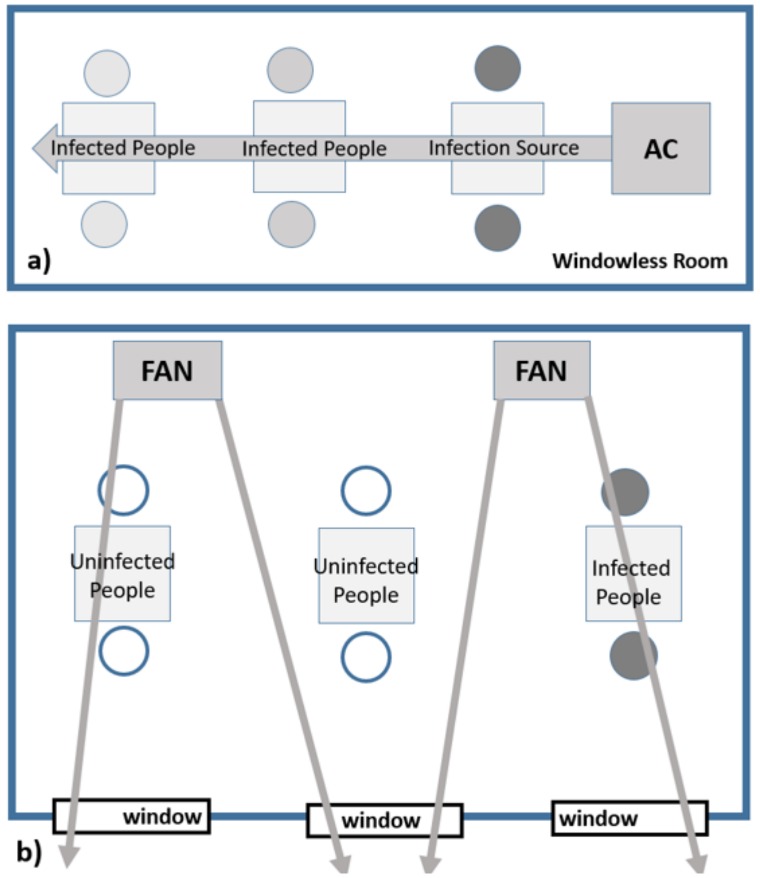


Figure 2. Direct and Dump Across and Out: A clear lesson from the Guangzhou restaurant case was that the direction of the air flow is critical, and the ability to dump load rapidly, for instance via windows. (Source: Roaf).

Figure 2 is a very simple representation of an extremely complex event that is brilliantly presented by Li et. Al. in their referenced paper and video on the subject. That simplicity is deliberate because it reflects a 'no-brainer' message, if you have opening windows that are open, viral load can be dumped out of them by well-directed air streams resulting in fewer people getting infected. If you are placing people in an airstream that is re-circulating virus laden air more people will get infected. The direction of the airflow can be critical, as can the load it carries. Increasing the speed of the air emanating from the vent of an air-conditioner may carry the virus in it even further, over a matter of seconds. Yet directionality is not stressed in much advice given to reduce spread indoors.

Air streams can be turbulent in spaces, wildly affected by simple actions like door opening, or waving sheets during bed making wards. Theoretical studies can convincingly demonstrate directions of flow in models, but in reality the placing of a chair, people or piece of equipment in the space can cause unpredicted reactions in the air movements. Pathways of an airborne virus can get into many nooks and crannies including behind face masks of workers, like those in food packing plants who stand in long production lines with cold air blown over them from one worker to the other.

A paper published in June 2020 clearly demonstrated the permeation of COVID-19 through air-conditioning ducts in a hospital in Oregon(13). The study demonstrated the presence of viral RNA in air handlers raising the possibility that viral particles can enter and travel within the air handling system of a hospital, from room return air and back into supply air ducts, despite being passed through high efficiency MERV-15 filters.

These findings were reinforced during a recent aerosol borne outbreak in a Dutch nursing home. Seventeen (81%) residents from one ward with a recycling air ventilator, and two air conditioners were diagnosed with COVID-19 and subsequently seventeen (50%) healthcare workers (HCWs) of the same ward also tested positive. By contrast, all tests of the one hundred and six HCWs and ninety-five residents in the six other wards with mechanical fresh air ventilation only were negative. CoV-2 RNA was detected in dust present on the mesh of the living room air conditioners of the ward, and in the block filters of the ventilation cabinets. The authors of the study called for others to take into account the possibility of such fatal aerosol transmission in healthcare facilities, and other buildings where ventilation systems recirculate unfiltered inside air(14).

On the 9th July 2020 the admission that aerosols provide a significant pathway for viral spread came from the WHO, who subsequently gave advice on ways to reduce viral loads in buildings, including by simply open windows as recommended in the 6th July letter.

SUPER SPREADERS – RS AND KS

In late February when the US had less than 20 known cases, the drug company Biogen held its annual conference in Boston, from which at least 97 people who attended the conference of 200 people, or lived with an attendee, were infected. Around then in Daegu, South Korea, just one woman, dubbed Patient 31, generated more than 5,000 known cases in a 'megachurch cluster' that has been graphically, brilliantly presented by Reuters. But very often those infected fail to pass on the virus or do so to very few people. Researchers in New Zealand looked at more than half the confirmed cases in the country and found a staggering 277 separate introductions into the country from abroad in the early months, but only 19 percent of introductions led to more than one additional case.

These findings impact the understanding, and calculations of the spread of the virus. A large Indian study of over 500,000 cases demonstrated that spread comes not just in 'slow transmission' from one to a second person, who then takes two days to become infected. In reality one person can infect 10, 100 or even 5000 people during one single event, as in the Korean example.

The spread of the virus in populations is typically described and projected using its R0 value, the basic reproductive number of a pathogen, a measure of its contagiousness on average, based on the thinking that it will be passed from one person to the next. But SARS-CoV-2 often spreads stochastically in cascading superspreading events, in which new infections caused by a super spreader are more likely to be highly infectious, which exposes new persons to high viral loads[15].

This pattern of cluster spread is possibly better described not as a function of R, but by its *K* value, its dispersion rate, reflecting whether a virus spreads in a steady manner, or in big bursts caused by one person infecting many, all at once. At this point it is clear that SARS-CoV-2 is an overdispersed pathogen, meaning that it tends to spread in clusters. To keep tabs on infection spread, it makes sense to backwards trace from an event to understand its history and the conditions in which superspreading occurs, than to merely contact trace forwards to warn of its future spread.

In Korea and Japan a group of elite contact tracers do just this in order to help understand and control its spread. How does this affect building design? Japan now takes a cluster busting approach to define the conditions in which superspreading events occur and based on them now focusses on solutions related to the ventilation of spaces in cluster source locations. Japanese are told to avoid places where the three C's come together: Crowds; Closed spaces and Close contact[16].

Figure 3. Image from the graphic of the Boston, Biogen superspreading event
(Source: https://vis.sciencemag.org/covid-clusters/?te=1&nl=coronavrus-briefing&emc=edit_cb_20201030).

WHAT ADVICE IS OUT THERE TO STOP COVID-19 SPREAD IN BUILDINGS?

Medical experts tend to recommend hand washing, protective clothing, the use of tissues when sneezing or coughing, cleaning surfaces, spatial distancing, limiting lift occupants, and using face masks in public spaces to reduce SARS-CoV-2 spread.

Heating, Ventilating and Cooling (HVAC) engineers almost universally suggest the need to install expensive, high-efficiency, front end, particulate air (HEPA) and UV filters for HVAC systems, despite the fact neither have been demonstrated to universally prevent cross-infection, and several authorities warn that their use can produce ***a false sense of security***. In practice, in the HVAC systems of buildings, with their often dusty and difficult to reach ducts, have been shown to contain and transmit COVID-19, with evidence from outlets vents and surfaces. Related concerns are not dealt with in the related advice.

The main means engineers promote to reduce the viral load around occupants are to:
a) increase the distance between them, and
b) improve 'ventilation' in spaces which is taken typically to mean increasing air speeds in the spaces, which may, potentially, simply infect more people further from the source person or duct.

Architects, are often poorly trained in issues of Indoor Air Quality (IAQ) and natural ventilation and in the UK will probably turn to an engineer for advice. Some mention the importance of simply opening windows. In Japan where the designing professions work more closely together, architects have offered sensible on COVID-19 infection in homes. Since 2003 a Building Standards Law made a 24 hour ventilation system obligatory but these are known not to provide sufficient ventilation rates to lower viral loads indoors so they recommend keeping doors and windows open too to flush out pollution and pathogens, including in public buildings like schools while the air-conditioning is on, a common practice throughout Japan[5]. This is only possible of course, for buildings with opening windows.

On the 29th October 2020 the WHO put out a video explaining how important natural ventilation of spaces via window opening is to purge room air, even in some polluted situations. It asked that authorities take on board the urgent need to deal with outdoor pollution if COVID-19 is to be dealt with effectively via affordable natural ventilation[18]. The video was weak in its ambitions and delivery which is surprising since that organisation has produced an excellent Guide to Natural ventilation in Health Care Settings, freely available on-line[18].
Given that every home on earth now might be considered a Health Care Setting, this useful guide might serve to inform the design of many different building types in future. None of the available advice reinforces the key messages about the use of natural or mechanical measures to Direct and Dump air via open windows, either Across spaces

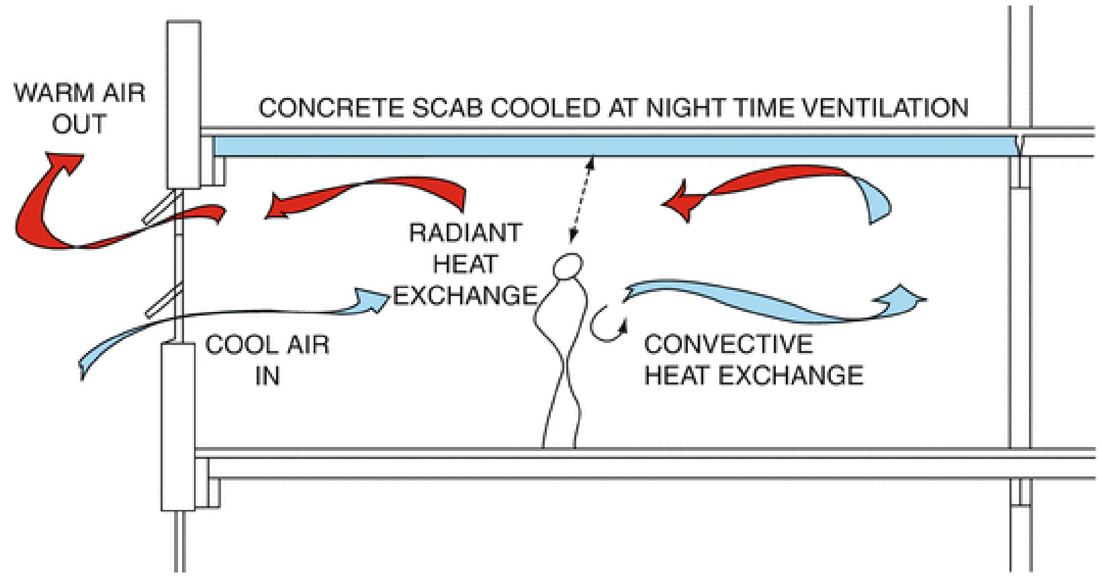


Figure 4. Direct and Dump Up and Out. Thermal buoyancy was traditionally used to remove aerosol borne pathogens away from patients in hospitals and could still be, requiring higher floor to ceiling heights, combined with high and low level window openings[17].

Figure 5. The Queen Elizabeth hospital in Glasgow opened in 2015, with no opening windows and serious ongoing nosocomial infection problems.

using air pressure, or Upwards using the buoyancy of warm air.

BRITTLE BUILDING SYNDROME: BUILDINGS WITHOUT OPENING WINDOWS

The £842 million Queen Elizabeth University Hospital in Glasgow (Figure 5) was opened in 2015 without opening windows and has subsequently suffered from various HVAC related deaths sourced to airborne pathogens. The Scottish government held an enquiry into whether the building was fit for purpose, less than four years after it opened[19]. Of course it was not designed to be Prepared for a Pandemic. Patients are assured, however, that they can all have '*access to an i-pad if they want to talk to their relatives*'.

The sheer madness of designing a hospital without opening windows must now be clear to the Scottish Government, and even more so for all in our profoundly unpredictable world. The many costs of wrong design choices are becoming desperately clear to many:

- **People will litigate against venues that infect them**. A Multi-million dollar settlement was paid out by SOM architects for poorly designed condominium complex in California with inadequate ventilation to prevent serious overheating indoors[20].Ventilation systems that provide insufficient ventilation or contaminated pathways are equally liable to such actions. Buildings like the Dutch Nursing Home in which many died, or the QE2 hospitals, where a child who died unnecessarily from a pathogenic infection transmitted from pigeon shit on the roof via a ventilation duct.
- **Climate weather events and trends** causing power outages and flooding have already led to horrendous tragedies like the abandoned patients in the blacked-out, flooded hospitals of New Orleans during Hurricane Katrina, or the uninhabitable apartment towers of flooded Manhattan, without opening windows or power that became putrid when still occupied for day without opening windows. That tragedy led to the plea by the New York Urban Green Council for at least 25% opening windows in all residences in Manhattan, in the wake of Hurricane Sandy[21].
- **Unreliable power supply systems** have led to ever increasing regional and national power system failures that design engineers trivialise because they have put contingency planning like 24 to 48 hours power back up systems. This author pleaded with WRM Engineers in the 1980s not to put in fixed windows in the new BASRA teaching hospital, and was met with such arguments. Months and years of blackouts ensued across Southern Iraq as a result of wars in the region. People are blindsided by what they cannot imagine.

HOW DID IT COME TO THIS? THE EMPEROR HAS NO CLOTHES

Traditional hospitals were built with high ceilings and large windows to ensure the removal of infectious pathogens away from patients, and to reduce cross infection rates. Every year modern hospitals become more highly serviced and more expensive to run, taking valuable finance away from paying front line medical staff, to pay for ever more mechanical servicing in buildings. Their architecture is pared back, with smaller rooms, with lower ceilings, fixed windows that don't open, to make them cheaper to build but more likely to become toxic sources of cross-contagion. Many modern hospitals and schools are now built in the UK under Public Private Finance Schemes, under which the developers are liable for the running and maintenance costs of the estate for 20-25 years, and many are designed to operate most successfully within that time window. Who pays when the hospital is sued for nosocomial infection deaths?

It is time to be honest. This cannot go on as we head into a hotter, more unpredictable and pandemic-riven future. It is time to say that The Emperor of Building Regulation and Standards has No Clothes.

Indoor Air Quality and Comfort Standards have over the last half century been hijacked by the Heating, Ventilating and Air Conditioning (HVAC), through a political system of patronage, lobbying, and the scientific blindsiding of politicians.

Most modern building developments are typically built to be fast in construction and profitable. They are shaped by four key drivers:

1. What Building Regulations require

2. What the Planners consider to be visually acceptable

3. What building developers want

4. The limitations imposed by the almost universal use of building design simulation design tools tend to steer users away from naturally ventilated designs, or the use of thermal storage in buildings.

Only one single page in the 64 page UK Building Regulations on Ventilation even mentions windows[23], with nothing included on natural ventilation for night-time cooling, over-heating mitigation, emergency ventilation during power blackouts, or reduction of indoor contaminants and pathogens. The regulations suggest opening windows might be useful in purging room air, of what is not said. In the UK the Building Regulations Advisory Committee, is convened by the Technical Policy Division of the Ministry of Housing, Communities and Local Government and chaired by the technical Director of the Chartered Institute of Building Service Engineers (CIBSE), with no architects, planners, health professional on it amongst its remaining cohort of fire engineers and developers.

In the USA air quality regulations are now written as the ASHRAE (American Society for Heating Refrigeration and Air-conditioning Engineers) Standards, after the profession that drafts them. They were originally developed there by the National Bureau of Standards, founded in 1901, and as late as the 1970s and 1980s they were overseen and advised by balanced panels of experts, including physiologists, architects, scientists, engineers and manufacturers.

The interests of the Air-Conditioning industry permeate the green building movements around the world, as has happened with the US LEED rating scheme for 'green buildings; which was co-developed by the Director of Environmental Marketing at the Carrier air-conditioning company. Under LEED it was mandatory to have a central AC system to be eligible for Platinum status, and precluded gaining points for the natural ventilation of buildings by simply opening windows[24].

The story of how American buildings Standard and Regulations were sub-subsumed by the HVAC industry has been well told elsewhere in books by Ackerman and Cooper, and the spread of this influence has been perpetrated via the International Standards Committees to national regulations across the world.

The extent to which this situation cannot be allowed to continue might be measure in COVID-19 deaths in poorly, and at times dangerously, ventilated spaces across the planet.

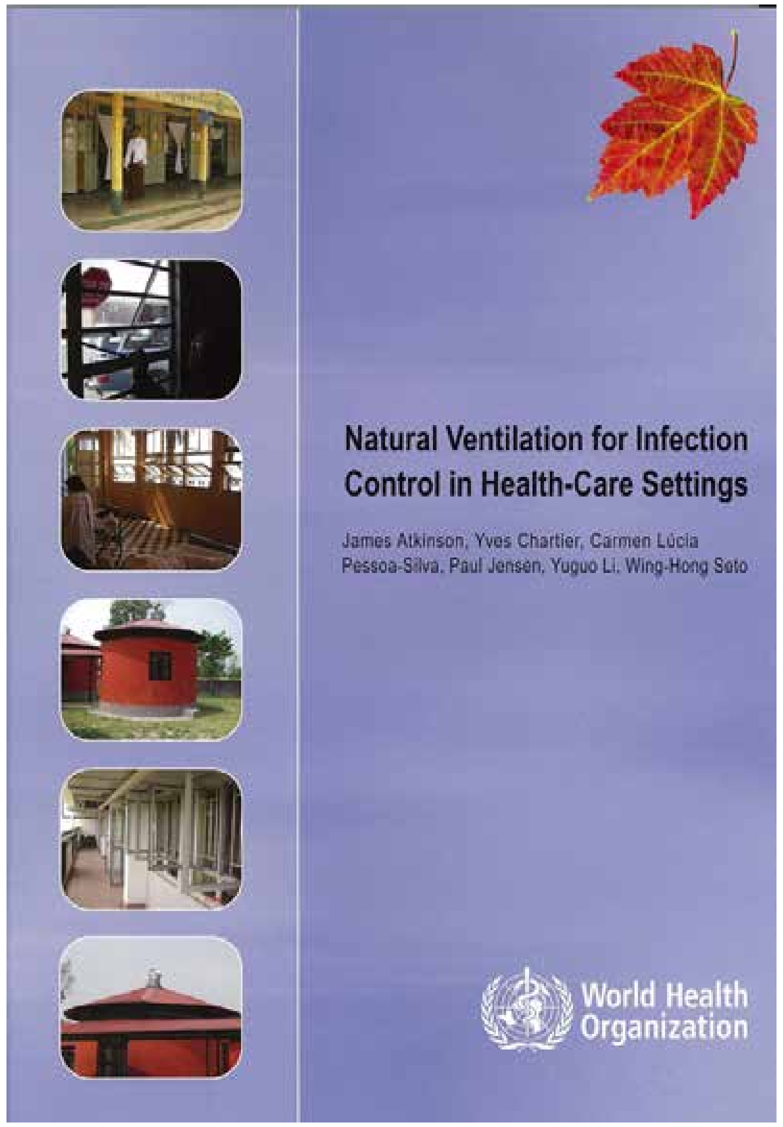
AFFILIATION BIAS IN THE REGULATORY SYSTEM

HVAC engineers have always been, and continue to be almost universally, paid according to the amount of HVAC equipment that goes into a building, providing a clear and positive incentive to put more in. Ever since engineers started writing the rules, regulations and standards for buildings more machines have been required to be installed in them to comply, be they commercial, public or domestic buildings leading to higher energy consumption, and significantly greater carbon emissions from them[25]. Competing systems like the use of natural ventilation via opening windows for purging of room air and also comfort cooling have been effectively side-lined by many HVAC regulators.

Many architects today are poorly educated on issues of building performance, having passed responsibility for it to engineers from the late 20th century onwards, and themselves been often side-lined in the design process regarding building performance[26]. This may explain why UK architects, for instance, typically earn much less than HVAC engineers, brick-layers, plumbers and even scaffolders.

An exhaustive study of the public commentary in the California environmental tobacco smoke risk assessment and Washington and Maryland indoor air regulations in the 1990s found evidence of systemic biases in the use of the process by critics and supporters of regulations using different criteria to evaluate the scientific evidence. It was found that various interests socially constructed evidence to support their predefined positions. At one point the tobacco industry suggested that ventilation is a very good control measure for environmental tobacco smoke, referencing ASHRAE Standard 62-1989, just as the HVAC industry is now promoting higher airflow rates to reduce viral load in spaces, despite the fact that most systems in larger buildings may simply be working with recirculated air so further forcing infections on a wider range of people[27].

Those promoting the harmlessness of passive smoking indoors used industry-sponsored symposium proceedings, or peer reviewed journal articles of lower quality to support their criticisms of the science of those who did not support their views. The study confirmed the findings of previous research that the attitudes of experts were influenced by affiliation bias and recommended that their data and the sources of research controversies should be independently investigated. Above all they highlighted risks arising from the different interest groups using different criteria to evaluate the research evidence and the dangers of not fully disclosing the special interests of the determination process, including those from corporate, public health and environmental groups. What was of paramount importance was that the policy and risk assessment process was strictly controlled to eliminate influence of such affiliation bias and that the problem must be seen as a body of evidence as a whole, rather focus on the minutiae of individual studies. Questions need to be asked. Who was on the WHO expert's committee that continued to deny that COVID-19 is spread by aerosols and might they have knowingly, or unwittingly, suffered from ***affiliation bias***?



See Reference (18)

POOR SCIENCE CLOSES WINDOWS

A large number of profound flaws in the apparently robust IAQ science are used to keep windows closed, including:

1. **Flawed methodologies used to minimise comfort zones to preclude natural ventilation.** The use of flawed steady state methods to calculate the narrow thermal comfort limits that oblige designers to install mechanical HVAC into buildings to provide comfort are widely used[28]. A far wider range of adaptive indoor temperatures are perfectly safe and acceptable, and promoted through building regulations in many countries now including The Netherlands and Brazil[29].

2. **Building Classifications to promote AC.** That more narrowly controlled temperatures in 'higher class' buildings (more expensive and more HVAC in them) are promoted as beneficial to health is based on a fallacy exploded by physiologists in recent years who demonstrated that varying temperatures help keep the venous systems of the body more active and healthy[30].

3. **Carbon dioxide** is used as a proxy for either Indoor Air Quality or levels of pollution in a room or to inform the control of ventilation systems. CO_2 is not a pollutant, as is presented by many HVAC professionals. In 1858 Max von Pettenkofer suggested 1000ppm as being a maximum threshold for unhealthy levels of the gas and this figure has become enshrined into architectural and engineering health guides over the last century. CO_2 levels in many of our own bedrooms will exceed 1000ppm every night, and the Portuguese have been found to be perfectly happy to be working daily in offices with CO_2 levels of 1000 to over 3000ppm[31]. The cross infection of a ward in the recent Dutch case study showed that the use of CO_2 as a proxy led to more infections as the 'efficient' AC / Ventilation system was set to change from re-cycled air to fresh outdoor air when it recorded CO_2 above 1000ppm. The patients were elderly, shallow breathers, so that level was never exceeded so the virus rich environment kept getting richer till nearly all in it became infected[14].

4. **Low airspeeds required to preclude natural ventilation.** The low airspeeds that are included in regulations are carefully designed to preclude the fresh, and gusty conditions often produced by opening a window, despite the fact that for cooling people in hot weather gusty air-streams are often more effective.

5. **Productivity** enhanced at the lower temperatures as provided by AC systems? The shaky research produced to back up this, and many similar productivity assumptions, was highlighted recently is a letter signed by ten international experts in the field who were deeply concerned by the weak science of the type that underpins related regulations[32]. They expressed their surprise at how far scientists are prepared to generalise from such a small, north European study in a highly contrived laboratory setting to general advice for people working in very different climates and countries. It is those that promote such shaky science that are to be found in the regulation and standards generating rooms that ask a very high entry fee to be part or, usually paid for by interested industrial partners.

6. **Sick Building Syndrome (SBS)** does not attract industry much funding nowadays as it has long been known that SBS symptom prevalence is significantly higher in air-conditioned buildings than in buildings with simple mechanical ventilation and no humidification[33].

POOR SCIENCE CLOSES WINDOWS

1. **Flawed methodologies used to minimise comfort zones to preclude natural ventilation.**
2. **Building Classifications to promote AC.**
3. **Carbon dioxide used as a proxy**
4. **Low airspeeds required to preclude natural ventilation.**
5. **Productivity enhanced at the lower temperatures as provided by AC systems?**
6. **Sick Building Syndrome (SBS) study neglected.**

MICROBES AND MODELS

Buildings are wickedly complex. There is no such thing as a single comfort temperature for everyone. The microbial ecological phenomena in every single building, including importantly its moisture content, is different from all others and will result in different health outcomes for similar exposures to a pathogen[34].People within buildings all behave differently as shown in a study of a hundred homes in Scotland, each with its own distinct microbiological character, in both species and number of cultivable microbes. But commonalities exist as in the Scottish example above, and the strongest signal reported there was that homes that reported opening windows more often were strongly associated with lower numbers of Gram-negative organisms at indoor sites[35].

When modelling buildings it is important to understand that selected examples cannot be used to provide general solutions. Some basic principles can be extrapolated from modelling exercises, for example quoted research above demonstrates that perhaps the most effective, affordable method to reduce viral load in a space is generally is via the use of natural ventilation systems to dump viral loads from spaces in buildings to reduce morbidity and mortality of occupants while providing a comfortable and healthy environments. Using this finding we can begin to develop ways to improve the Preparedness of our Buildings for future Pandemics.

THE NEED FOR BIG PICTURE THINKING ON VENTILATION

'We are ruled by ideas and very little else... But the rule of ideas is only powerful in a world that does not change. Ideas are inherently conservative. They yield not to attack of other ideas... but to the massive onslaught of circumstances with which they cannot contend'[36].

John Maynard Keynes sheds light on where we stand today, losing a battle against COVID-19 in the midst of the massive onslaught of a pandemic 's circumstances, in a rapidly heating world. Building regulations are developed reactively after great plagues or fires or floods. Now is the time to re-write our building regulations that were based on 20th century assumptions that are already visibly dated. We need to envisage Step Changes now in building design and servicing to ensure that we are much better prepared for our different future, than we were when SARS-CoV-2 hit us just nine months ago. Tools to measure, understand and model the complex systems involved in the multi-dimensional issues around sustainability or resilience, realistically, do not exist. The experts we hear in the media often dwell on risk, avoiding the more problematic issues around uncertainty:

'Risk is where we know what the possible outcomes are and can estimate their probabilities. Uncertainty is about where we are unsure of the probabilities of particular outcomes. This is important because there is too often a tendency to 'close down' towards risk. Pretending to know the probabilities. Yet this is often not realistic in practice, as models and estimates are confounded by uncertainties. In cases where systems are complex, interacting and non-linear, a narrow risk-based approach is inappropriate[37].

We are surrounded by people selling us certitudes from modelled studies. It is these certitudes that have created an urban and built environments, with their fixed windows and over-mechanised buildings that are extremely unprepared for pandemics, heatwaves, flooding, extreme weather events, power grid and other infrastructural failures. Too often apparently comprehensive modelling exercises fail because of affiliation biases that nudge the assumptions underlying them in this way or that, to promote the selling of this product or that. People are convincingly sold highly calculated Turkeys, like the purchasers of homes in an award winning Sustainable Community in the Arizona desert that was hailed by all as leading edge and a perfect home for eco-worriers, except that it had no water rights for that area[38]. One conveniently omitted variable and the calculations collapse. Lessons abound from the historic failures of such simple, and more complex societies in which complexity itself can cause failure. Placing systems in a straitjackets of constancy can cause fragilities to evolve that can destroy whole ecosystems[39]. To cope with this, and future pandemics, we have to evolve rapidly to survive.

The daily changes in the trajectories of cases of the SARS-CoV-2 pandemic emphasise the limitations of modelling for all to see and understand. Reality often pivots on the turbulence caused by a butterfly's wings, or the words or actions of an influencer. Herein also lie huge opportunities, as Ayres pointed out in his book on Turning Points, that simple quantifiable models are not be adequate to identify timings, and other attributes of turning points, but that: naive intelligence and intuition may be the best tool for coping with a very complex and non-deterministic future[40]. With that proposal in mind the final section of this paper includes my recommendations.

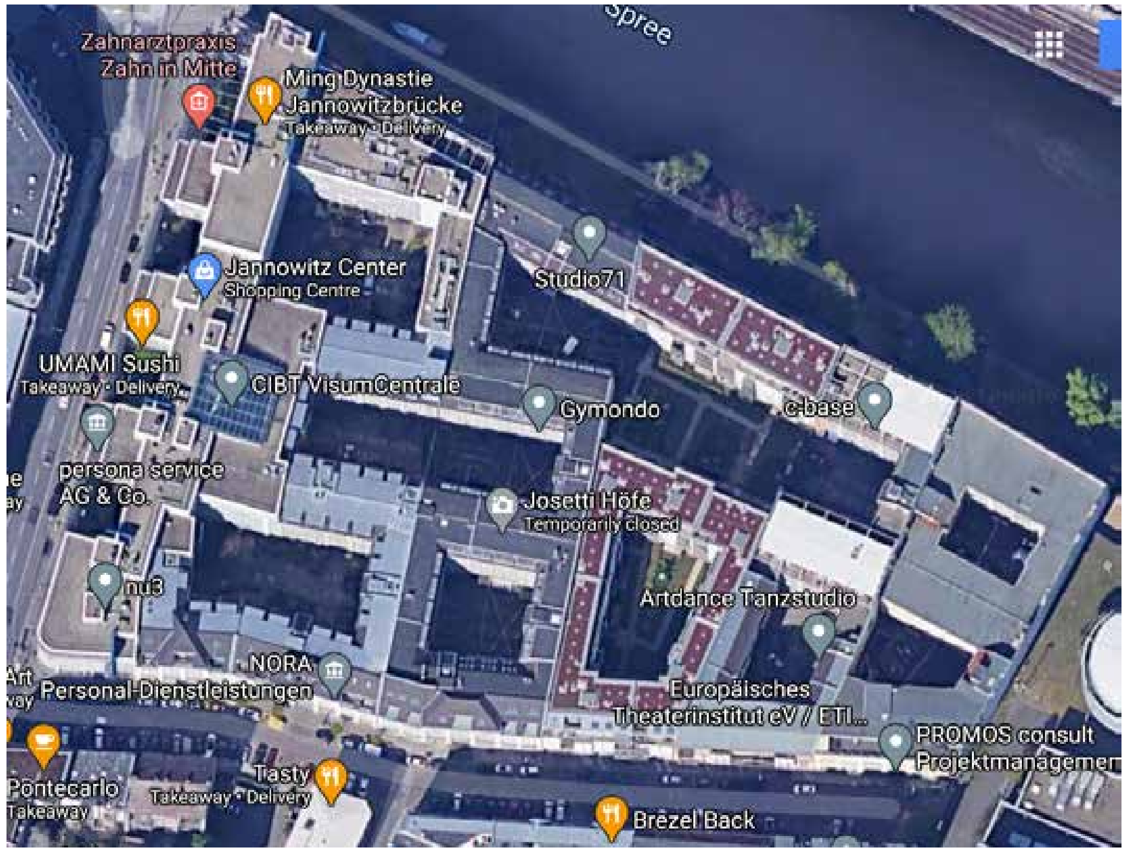


Figure 6. Google aerial view of a Berlin building block, in a city where urban ordinances ensured that the depth of building footprints enable natural ventilation and daylighting of most internal spaces (Source: Googlemaps).

A key lesson to take that forward is: what really matters is the PROCESS of making change happen. Building resilience and preparedness is a 'Super Wicked' problem, riddled with barriers to the evolution of the system imposed by those with vested interests in retaining the status quo of a non-evolving system. In 2009 Lazarus proposed that: *To be successful over the long term, climate change legislation will need to include institutional design features that significantly insulate programmatic implementation from the undue influence of powerful political and economic interests propelled by short-term concerns*[41].

The **"Recommendations for Preparing the Built Environment for Pandemics – Summary for Policy Makers"** (see next page) may not happen overnight, but are essential if we are to ensure that brittle, unprepared buildings do not increasingly kill their occupants, as they have been shown to do in some of the cases presented above. These actions will not be cheap and the prospect of changing the Status Quo here will be horrific for many whose influence at the heart of government has been so effective in steering the super-tanker of development for the last half century. But the cost of not acting now will be much higher. Many of our modern building are so totally dependent on installed HVAC systems that when they do go wrong, they can financially break companies. In 2003 Hilton Hawaii reopened the once mould-ridden air-conditioning system in a single building, the Kalia Tower, that cost US$55 million in repairs and lost revenue over 14 months[42]. This hints at the scale of the financial implications of acting, and not acting. What if the next pandemic is even more easily spread by aerosols? Abandoned hospitals and Health Care Facilities?

The good news is that increasing reliance on natural ventilation in buildings will not only reduce viral loads, and consequently cross-infections in them, but also reduce their energy running costs, maintenance costs, overheating in them, and importantly CO_2 emissions from them. Whole life cycle costings can prudently underpin financial calculations when developing a new generation of regulations.

RECOMMENDATIONS FOR PREPARING THE BUILT ENVIRONMENT FOR PANDEMICS

SUMMARY FOR POLICY MAKERS

by Prof. Susan Roaf

1. **Nationally.** Establish a national, multi-disciplinary task force of independent experts to review all building regulations with a view to reframing them to enhance the resilience and preparedness of the built environment in the face of future pandemics and climate change. All members must transparently declare affiliations and conflicts of interest.

2. **Urban scale.** Reduce urban pollution so that people can safely open windows for ventilation, comfort cooling and to purge pathogen loads.

3. **Urban scale.** Amend Planning Laws to ensure building footprints are narrow enough to enable all habitable rooms to have opening windows and natural light, as was enshrined in the Berlin town planning statues and has resulted today in that city being capable of being naturally ventilated.

4. **Urban scale.** Undertake wind-scaping studies of cities to prevent or remove buildings that block natural airways through the city, flushing out heat and pathogens.

5. **Urban scale.** Create climate refuges across the city where people can get outdoors into a thermally safe environment, while socially distancing, during extreme heat waves or pandemics.

6. **Buildings.** Change National and Local Building Regulations and Guidelines to ensure that at least 25% of all building windows are openable and all habitable rooms can be naturally ventilated.

7. **Buildings.** Legislate for the universal adoption of Adaptive Thermal Comfort Standards for building that allow for the natural ventilation of buildings.

8. **Buildings.** Instigate a building classification system that promotes naturally ventilated and mixed mode buildings before fully air-conditioned ones.

9. **Buildings.** Instigate a modal shift in heating and cooling away from air-driven HVAC systems that promote pathogen transmission between spaces and people, toward radiant systems where pathogens can be removed by wiping surfaces, and un-reachable and un-cleanable ducts are minimised, or eliminated, in systems.

10. **Buildings.** Increase floor to ceiling heights in hospitals and schools to enable effective buoyancy-driven displacement ventilation to exhaust lighter aerosols from high level windows / openings. Lower walls surfaces can be disinfected of larger droplets by wiping.

11. **Buildings.** Provision for shading, security and insect screens and ease of occupant usability of windows to be required at the design stage.

12. **Buildings.** Health and care facilities should provide separate, safe, patient/visitor meeting spaces outwith the naturally ventilated rooms and wards, or develop systems whereby windows can be closed for 'through the window' encounters during Lockdowns.

13. **Buildings.** Make natural ventilation training mandatory for all architects and engineers.

14. **Transport.** Install opening windows in all public transport including buses, trains and trams for use either to reduce pathogen loads by providing good cross ventilation en route.

Susan Roaf, BA, AA Dipl., PhD, ARB, FRIAS is Emeritus Professor of Architectural Engineering at Heriot Watt University, Edinburgh.
An award winning author, architect and solar pioneer, she currently works and publishes on thermal comfort, passive design and climate change. In practice she was part of the design team for hospitals in Iraq, including a the 1986 teaching hospital in Basra. A number of her publications cover the issue of effective ventilation of buildings and advanced natural ventilation technologies.

References

(1) Lidia Morawska, Donald K Milton, It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19), Clinical Infectious Diseases, ciaa939, https://doi.org/10.1093/cid/ciaa939

(2) Lewis, Dyani (2020). Mounting evidence suggests coronavirus is airborne – but health advice had not caught up. Nature News Feature 20 July 2020. Accessible on: https://www.nature.com/articles/d41586-020-02058-1

(3) Li, Y., X. Huang, Yu, I.T.S. Yu, T.W.Wong and H.Qian (2005). Role of air distribution in SARS transmission during the largest nosocomial outbreak in Hong Kong, Indoor Air, https://doi.org/10.1111/j.1600-0668.2004.00317.x

(4) Escombe, A. Roderick, Clarissa C Oeser, Robert H Gilman, Marcos Navincopa, Eduardo Ticona, William Pan, Carlos Martínez, Jesus Chacaltana, Richard Rodríguez, David A. J Moore, Jon S Friedland, Carlton A Evans (2007). Natural Ventilation for the Prevention of Airborne Contagion, PLOS Medicine, https://doi.org/10.1371/journal.pmed.0040068

(5) Hayashi. M., U. Yanagi, K. Azuma, N. Kagi et a. (2020). Measures against COVID-19 concerning Summer Indoor Environment in Japan, Japan Architectural Review, vol 3. No. 4., pp.423-434.

(6) Nicol, F., M. Humphreys and S. Roaf (2012). Adaptive Thermal Comfort: Principals and Practice, Earthscan/Routledge. ISBN 978-0-415-69159-8.

(7) Ma, Jianxin, Xiao Qi, Haoxuan Chen, Xinyue Li, Zhang Zheng, Haibin Wang, Lingli Sun, Lu Zhang, Jiazhen Guo, and Lidia Morawska, et al. (2020). COVID-19 patients in earlier stages exhaled millions of SARS-CoV-2 per hour. Clinical Infectious Diseases, ISSN 1058-4838.

(8) van Doremalen, N., T. Bushmaker and D.H. Morris (2020). Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1, New England Journal of Medicine letter 17th March, 382, 16.

(9) Bahl, Prateek, Con Doolan, Charitha de Silva, Abrar Ahmad Chughtai, Lydia Bourouiba, C Raina MacIntyre, Airborne or Droplet Precautions for Health Workers Treating Coronavirus Disease 2019?, The Journal of Infectious Diseases, jiaa189, https://doi.org/10.1093/infdis/jiaa189

(10) Gormley, M., T.J. Aspray and D.A. Kelly (2020). COVID-19: mitigating transmission via wastewater plumbing systems, Lancet 2020 volume 3, p. 643. https://doi.org/10.1016/ S2214-109X(20)30112-1

(11) Al-Ansary LA, Bawazeer GA, Beller E, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Part 2 - Hand hygiene and other hygiene measures: systematic review and meta-analysis.
medRxiv 2020: 2020.04.14.20065250

(12) Li Y, Qian H, Hang J, Chen X, Hong L, Liang P, et al. Evidence for probable aerosol transmission of SARSCoV-2 in a poorly ventilated restaurant. medRxiv. 2020. https://www.medrxiv.org/content/10.1101/2020.04.16.20067728v1

(13) Horve, Patrick F., Leslie Dietz, Mark Fretz, David A. Constant, Andrew Wilkes, John M. Townes, Robert G. Martindale, William B. Messer, Kevin G. Van Den Wymelenberg (2020). Identification of SARS-CoV-2 RNA in Healthcare Heating, Ventilation, and Air Conditioning Units, medRxiv preprint doi: https://doi.org/10.1101/2020.06.26.20141085

(14) de Man, Peter, Sunita Paltansing, David S. Y. Ong, Norbert Vaessen, Gerard van Nielen and Johannes G. M. Koeleman (2020). Outbreak of Coronavirus Disease 2019 (COVID-19) in a Nursing Home Associated With Aerosol Transmission as a Result of Inadequate Ventilation, Clinical Infectious Diseases, August, https://doi.org/10.1093/cid/ciaa1270

(15) Beldomenico, Pablo M. (2020). Do superspreaders generate new superspreaders? A hypothesis to explain the propagation pattern of COVID-19, International Journal of Infectious Diseases, Vol. 96, pp. 461-463.
https://doi.org/10.1016/j.ijid.2020.05.025

(16) Tufekci, Zeynep, (2020). This Overlooked Variable Is the Key to the Pandemic-It's not R, published on line by The Atlantic, September: https://www.theatlantic.com/health/archive/2020/09/k-overlooked-variable-driving-pandemic/616548/

(17) Yang T., Clements-Croome D.J. (2012) Natural Ventilation in Built Environment. In: Meyers R.A. (eds) Encyclopedia of Sustainability Science and Technology. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-0851-3_488.
Image from this book.

(18) Atkinson, James, Yves Chartier, Carmen Lúcia Pessoa-Silva, Paul Jensen, Yuguo Li and Wing-Hong Seto (Eds) (2009). Natural Ventilation for Infection Control in Health-Care Settings, WHO Guidelines. ISBN 978 92 4 154785 7.
Available on: https://www.who.int/water_sanitation_health/publications/natural_ventilation.pdf

(19) Jessle, E. (2019). Inquiry ordered into design of IBI's tragedy-hit Scottish hospital, Architect's Journal, https://www.architectsjournal.co.uk/news/inquiry-ordered-into-design-of-ibis-tragedy-hit-scottish-hospital

(20) http://scocal.stanford.edu/opinion/beacon-residential-etc-assn-v-skidmore-owings-merrill-34333

(21) http://urbangreencouncil.org/sites/default/files/brtf_26-_ensure_operable_windows.pdf

(22) hobday R. A. and S.J. Dancer (2013). Roles of sunlight and natural ventilation for controlling infection: historical and current perspectives, Journal of Hospital Infection, Vol. 84, Issue 4. DOI: https://doi.org/10.1016/j.hhin.2013.04.001

(23) H.M.Government (2010). Building Regulations, Part F: Ventilation, Approved Document.

(24) Shaviv, E. (2008). Passive and Low Energy Architecture (PLEA) VS Green Architecture (LEED), Paper 371 in Proceedings of the PLEA 2008 Conference, Dublin.

(25) Cass, N., and E. Shove (2018). Standards, whose Standards?, Architectural Science Review, vol. 61.issue 5, pp. 272-279, https://doi.org/10.1080/00038628.2018.1502158.

(26) Roaf, S. (2020). Thermal Comfort and it regulation, Proceedings of the 11th Windsor Conference on Comfort. Available on. www.windsorconference.com. ISBN: 978-1-9161876-3-4

(27) Bero L.A (2002). Case studies of the role of research in the development of indoor air policies, in Proceedings of the Indoor Air Conference, Ed. Hal Levine, Monterey, Vol. 2, pp.1-11. ISBN: 0972183205 9780972183208

(28) Humphreys M., F.Nicol and S,Roaf (2015). Adaptive Thermal Comfort: Memories, Foundations and Analysis, Earthscan. London.

(29) Roaf, S., F. Nicol and Vertaling Peter van den Engel (2020). Acceptabele temperaturen in natuurlijk geventileerde gebouwen, TVVL magazine / onderzoek & cases nr. 05 / oktober, pp. 62-70.

(30) Van Marken Lichtenbelt, W., Hanssen, M., Pallubinsky, H., Kingma, B., Schellen, L. (2017) Healthy excursions outside the thermal comfort zone, Building Research and Information, Taylor and Francis 3218 (September) pp 1-9.

(31) Humphreys, M.A., F. Nicol. and K. McCartney (2002). An analysis of some subjective assessments of indoor air-quality in five European Countries, Proceedings of the Indoor Air Conference, Ed. Hal Levine, Monterey, ISBN: 0972183205 9780972183208

(32) de Dear, R., C. Candido, G. Brager, H. Zhang, J. Toftum, Y. Zhu, S. Kurvers, J. Leyten, C. Sekhar and D. K. W. Cheong (2014). Indoor temperatures for optimum thermal comfort and human performance – Reply to the letter by Wyon and Wargocki, Indoor Air, John Wiley & Sons Ltd, doi:10.1111/ina.121065

(33) Seppänen, O. and W.J.Fisk (2002). Association of ventilation system type with SBS symptoms in office workers, Indoor Air, Vol.12, Issue 2, pp. 98-112.

(34) Nevalainen, A. (2002). Of Microbes and Men, Proceedings of the Indoor Air Conference, Ed. Hal Levine, Monterey, Vol 3, pp.1-10. ISBN: 0972183205 9780972183208

(35) Sharpe, T., McGill, G., Dancer, S.J. et al. (2020). Influence of ventilation use and occupant behaviour on surface microorganisms in contemporary social housing. Nature Scientific Reports, 10, 11841. https://doi.org/10.1038/s41598-020-68809-2

(36) J. K. Galbraith (1958). The affluent Society. 1999 Ed. published by Penguin Books, London, p.17.

(37) Scoones, I. and A. Stirling (2000). The Politics of Uncertainty Challenges of Transformation, Routledge. ISBN 9780367903350

(38) Roaf, S. (2013). Transitioning to Eco-Cities: Reducing Carbon Emissions while Improving Urban Welfare, Chapter 7 in Secure & Green Energy Economies edited by Young-Doo Wang and John Byrne, Transaction Publishers, Washington. ISBN: 9781412853750.

(39) Holling, C.S. (ed.)(1978). Adaptive Environmental Assessment and Management, John Wiley and Sons Inc., Chichester, p. 105.

(40) Ayres, R. U. (1999). Turning point: the end of the growth paradigm, Earthscan, London.

(41) Lazarus, R.J. (2009). Cornell Law Review, Vol. 94, pp. 1153-1234.
Available on: http://www.lawschool.cornell.edu/research/cornell-law-review/upload/Lazarus.pdf

(42) https://www.bizjournals.com/pacific/stories/2003/09/01/daily5.html

THE IMPORTANCE OF UNDERSTANDING AIRBORNE TRANSMISSION OF SARS-COV-2 AND EFFICIENT MEASURES FOR CONTROLLING AIRBORNE PANDEMICS

Abstract

This paper discusses on the evidence of the transmission of the SARS-CoV-2 virus of COVID-19 through air, which appears regulated by mechanisms occurring explosively, and at long distance, as well as on the protective measures that should be considered in order to prevent further transmission. Nevertheless, some uncertainties still exist regarding travelling distances, which call for validation exercises on the models used to derive protective measures. Therefore, we are currently developing an experimental study in order to effectively assess safe distances from potentially affected individuals.

“

The transmission of the virus of COVID-19 through air is regulated by mechanisms which are similar to measles, thus occurring explosively and at long distance. Validation exercises on the models used to derive protective measures are undertaken.

”

João F. P. Gomes, PhD, Professor Chemical Engineering, Dept. of Chemical Engineering, ISEL – Lisbon Polytechnic, Lisboa, Portugal

The transmission of the SARS-CoV-2, the virus of COVID-19 disease through air is regulated by mechanisms which are similar to measles, thus occurring explosively and at long distance. Therefore, it is important to notice the role of exposure by inhalation of virus present in micro droplets in short to medium range, from some meters to the dimensions of a room. However, the potential for long range transmission is currently, uncertain, and this has been the cause for adopting preventive containment measures. The main characteristics and mechanisms leading to the generation of respiratory micro droplets[1], survival of virus within micro droplets[2], transportation of microdroplets and its human exposure[3], as well as the aerodynamic fluxes transporting micro droplets in indoor environments[4], are already understood. The current perception that micro respiratory droplets bigger than 5μm, are deposited within 1m from the human emitter are, in fact, incorrect. Considering typical air velocities, a droplet of that size is able to travel for more than 10m, which is, usually, more than the typical size of rooms, and yet it has also to decay from a height of 1.5m: a droplet this size should have a dimension of, at least, 50μm, in order to fall within a circle of 1m around a person. Thus, the actual regulations from national health bodies, based on hand washing and observation of social distancing could be insufficient, as airborne droplets could travel to long distances and stay in the air while the virus is still active. This problem is particularly important in indoor environments with low ventilation and is aggravated in situations of high occupancy and for long exposures. Several studies have

demonstrated that the virus is released during respiration, talking, coughing and sneezing, thus resulting in the release of micro droplets small enough to stay in the air and, thus constitute on infection risk for distances between 1 and 2m away from infected individuals[5]. Naturally, micro-droplets are more concentrated in the low distance range and are related to non-symptomatic transmission[6]. Other studies have shown that airborne transmission is the most probable cause to explain the observed social infection pattern[7], whereas the virus of COVID-19 behaves as previously described, and therefore the risk is quite high in indoor environments, mainly those having high occupancy and low ventilation. Thus, the safety measures to be adopted so as to mitigate the airborne transmission comprise:

a) to provide enough efficient ventilation (supplying clean outside air, minimizing air recirculation), particularly in public building, indoor environments, schools, hospitals, health centres and nursing homes;

b) complement general ventilation with systems controlling airborne infection such as local exhaustion, air filtration through UV lights;

c) avoid overcrowding, particularly in public transport systems and public buildings, and maintain social distancing;

d) use of masks in indoor environments and even in overcrowded outdoor environments.

Thus, it is of paramount importance to be able to preview accurately of time and falling distances in indoor environments, which can be done by numerical simulation of dispersion. Although this is not a trivial problem, studies such as this, for very fine particles, started to be done from 1970 following the Chernobyl accident, whereas the decay of very fine particles was studied as the decay of radioactive species.
Previous epidemic surges of infectious corona virus, such as SARS and MERS, lead to the development of computational models[8], mainly based on fluid mechanic principles, in order to estimate the permanence of airborne droplets emitted from the human respiratory system, thus considering turbulent dispersion which can be treated by 3D discretization of finite elements. The COVID-19 pandemic has led to the development of several new models trying to describe this situation, in order to allow the estimation of safety distance from infected individuals. Nevertheless, no mathematical model is able to accurately preview the real situation if it has not been validated. The reliability of each model will be dependent from the imposed boundary conditions as well as input data, where the uncertainty is high as there are several factors involved some of them interdependent[9]. Validation is an unavoidable task, where the reliability of the obtained output cannot be assessed.
Currently, avoiding the validation of such models, has been adopted as the urge to estimate safety distances[10], but does not constitute the acceptance of results generated by models. It is already known that the SARS-CoV-2 virus has a size ranging from 80 to 140nm[11] and is able to be transmitted through airborne micro droplets expelled by human individuals while breathing, talking, coughing or sneezing. It is also known that both virus and micro droplets can condensate in nuclei such as airborne ultrafine particles[12].

Thus, if the distribution of ultrafine particles resulting from a release event in the vicinity of a human individual in known, it will be possible to know the evolution of the transmission cloud of the SARS-CoV-2 virus. By knowing the distribution of ultrafine particles, in terms of size, number and concentration, it will be possible to estimate accurately, distances from which the previous parameters are small enough to define safety distances from the individual who emitted the virus.

It should be noted that this approach is in accordance with the recommendations issued by standard committee CEN/TC264/W32 and the Cost Action 17136 – Indoor Air Pollution Network, both committees where the author is an active member.

Also, together with his research team he has been involved in monitoring ultrafine particles in outdoor environments[13], indoor environments and occupational, and developed a methodology consisting in determination of the number, size distribution, morphology and concentration (measured as the lung deposited surface area, use the ICRP model, validated by ACGIH, which is based in radioactivity dispersion[14]. This is the basis of the rationale of a research project, currently underway, based on field measurements that will be complemented with the analysis of collected ultrafine particles using electronic microscopy such as SEM, TEM and chemical composition by EDS and the assessment of heath impact in exposed individuals[15]. Therefore, using these specific monitoring equipment and the previously developed methodology, it will be possible to achieve the mapping of the cloud of ultrafine particles in an indoor environment from a human individual.

This methodology has been used, previously, with success, to estimate "safe" and "critical" regions in occupational environments[16].

This study will follow the same methodology, by monitoring ultrafine particles in indoor atmospheres which are the condensation nuclei for SARS-CoV-2 the virus of COVID-19, allowing to identify areas as "safe", "contaminated" or "susceptible of contamination", from human sources, as well as the safety distances from human individuals, with and without protective masks.

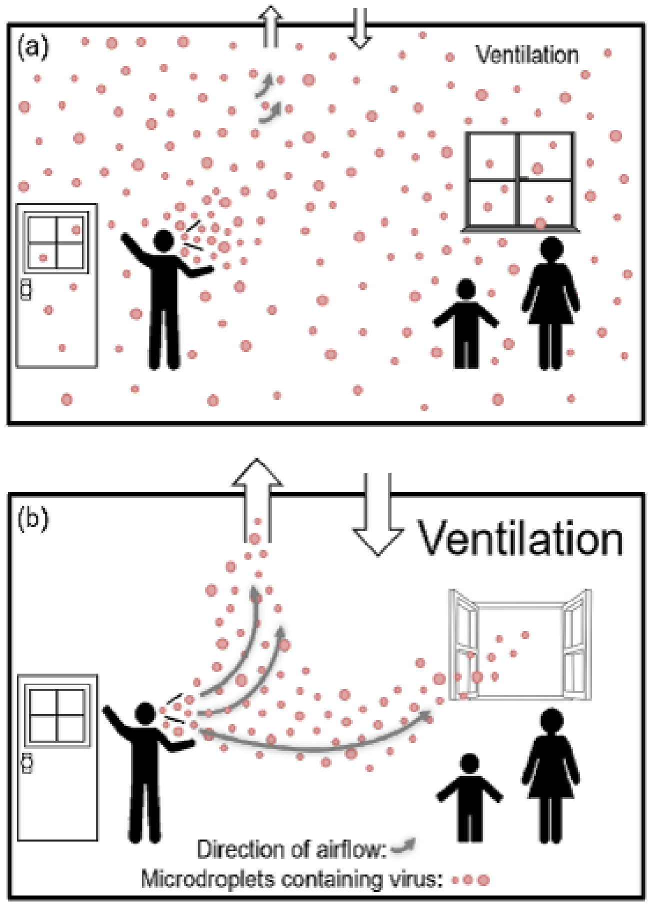


Figure 1. Distribution of respiratory microdroplets in an indoor environment with (a) inadequate ventilation and (b) adequate ventilation.

THIS RESEARCH PROJECT COMPRISES:

I) Mapping of clean indoor environments in what concerns concentration and size distribution of ultrafine particles: using NSAM and SMPS analysers, the mapping of concentrations and particles size distribution in a clean environment that will be considered ground zero;

II) Mapping of the evolution of the cloud of ultrafine particles in indoor environments from a simulated human emitting source: again using NSAM and SMPS analysers, the mapping of concentrations and particle size distribution previously characterized will be performed from a simulated human being. Tests will be repeated until a stabilized concentration could be attained, for situations with and without mask and, also, for different ventilation conditions. Ultrafine particles will also be collected by NAS analyser for further characterisation using electronic microscopy;

III) Data treatment: analysis and discussion of results previously obtained and, thus, the determination of zones having equal concentration and size of ultrafine particles;

IV) Model development: development of a simple numerical model describing the evolution of the transmission cloud of the virus of COVID-19 disease and validation of models previously developed on this subject.

Finally, the dissemination of project results will be made by the publication of the experimental results obtained within the development of the project, and its main conclusions in scientific peer-referred international journals, as we believe these conclusions are of utmost significance thus contributing to avoid the spread of the COVID-19 pandemic.

João Gomes was awarded a BSc, PhD and Habilitation in Chemical Engineering, from the Technical University of Lisbon, and is a full Professor of Chemical Engineering at ISEL – Lisbon Polytechnic, since 2006. Previously he was a research assistant in the Centre Chemical Processes at the Technical University of Lisbon, a research fellow at National Laboratories for Engineering and at the R&D Department of ISQ, a Portuguese inspection company where he was also Deputy Director, managing the Environmental Division. He lectured at the Technical University of Lisbon, Lusofona University and Atlantica University. His main research interests are Clean Processes, Air Pollution, Nanoparticles and Nanotoxicology.

References

(1) Modality of human expired aerosol size distributions, Journal of Aerosol Science. 42: 839/51 (2011).

(2) Influenza virus infectivity is retained in aerosols and droplets independent of relative humidity, Journal of Infectious Diseases.218: 739/47 (2018).

(3) Toward understanding the risk of secondary airborne infection: emission of respirable pathogens, Journal of Occupational Environmental Hygiene. 2: 143/54 (2005).

(4) Evidence of airborne transmission of the severe acute respiratory syndrome virus, New England Journal of Medicine. 350: 1731/39 (2004).

(5) How far droplets can move in indoor environments, Indoor Air. 17: 211/25 (2007).

(6) Close contact behaviour in indoor environment and transmission of respiratory infection, Indoor Air (2020).

(7) Severe acute respiratory syndrome beyond Amoy Gardens, Clinical Infectious Diseases. 58: 683/6 (2014).

(8) Computational modelling of aerosol deposition in respiratory tract, Inhalation Toxicology. 21: 262/90 (2009).

(9) The dry deposition of small particles: a review of experimental measurements, Atmospheric Environment 22: 2653/66 (1988).

(10) Epidemiology and transmission of COVID-19 in Shenzhen, China, medRxiv, Mar4 (2020).

(11) An analysis of the transmission modes of COVID-19 in light of the concepts of Indoor Air Quality, Univ. Coimbra, Coimbra, 2020.

(12) Association of airborne virus infectivity and survivability with its carrier particle size, Aerosol Science and Technology. 47: 373/82 (2013).

(13) Assessment of exposure to airborne ultrafine particles in the urban environment of Lisbon, Portugal, Journal of Air and Waste Management Association. 62:373/80 (2012).

(14) Notice on a methodology for characterizing emissions of ultrafine particles/nanoparticles in microenvironments, Energy and Emission Control Technology. 1: 15/27 (2013).

(15) Nanoparticle exposure and hazard in the ceramic industry: an overview of potential sources, toxicity and health effects, Environmental Research. 184: 109297 (2020).

(16) Determination of safe and critical nanoparticles exposure to welder in a workshop, Journal of Toxicological Environmental Health A. 80: 767/75 (2017).

THE CHARACTERISTICS OF HOSPITAL AIR DUST RESISTOME INDICATE THE NECESSITY TO CONTROL AIRBORNE ARG SPREAD

Abstract

In hospitals, the potential for airborne dissemination of antibiotic resistance genes, via air-conditioning systems, has not been under extensive scrutiny. Our research shows the importance of proper systems and surveillance, as air-conditioners can develop resistome, accumulate pathogens and disseminate them across rooms and notably in the outpatient hall.

In our newly published research (Chemical Engineering Journal 406 (2021) 126854[1], Figure 1), we developed a metagenomic-based method to study the transmission of antibiotic resistance genes (ARGs) via the air route in a hospital indoor environment. Besides metagenomic sequencing, we also applied microbial cultivation, PCR, and Nanopore whole genome sequencing to confirm the accuracy of data analyses in our method. Overall, the main findings support 1) plasmid-mediated ARG transfer can occur frequently among departments via air spreading; 2) hospital managers should pay attention to *Staphylococcus*, *Micrococcus*, *Streptococcus*, and *Enterococcus*, etc., and the eukaryotic resistances might be an overlook in the Hospital setting.

> ***"Currently, lots of effort has been made towards learning how micro-organisms colonize and migrate in the hospital's indoor environment, however, little is known about the possible indoor air transmission route for antibiotic resistance genes.***
>
> ***Metagenomic research ... indicated the hospital air-conditioning system can form resistome, and accumulate pathogens which are then disseminated via air flows, notably in outpatient waiting rooms."***

Yu Xia, PhD, Assistant Professor, Southern University of Science and Technology, Guangdong, China;

Xiang Li, PhD, Research Assistant Professor, Southern University of Science and Technology, Guangdong, China;

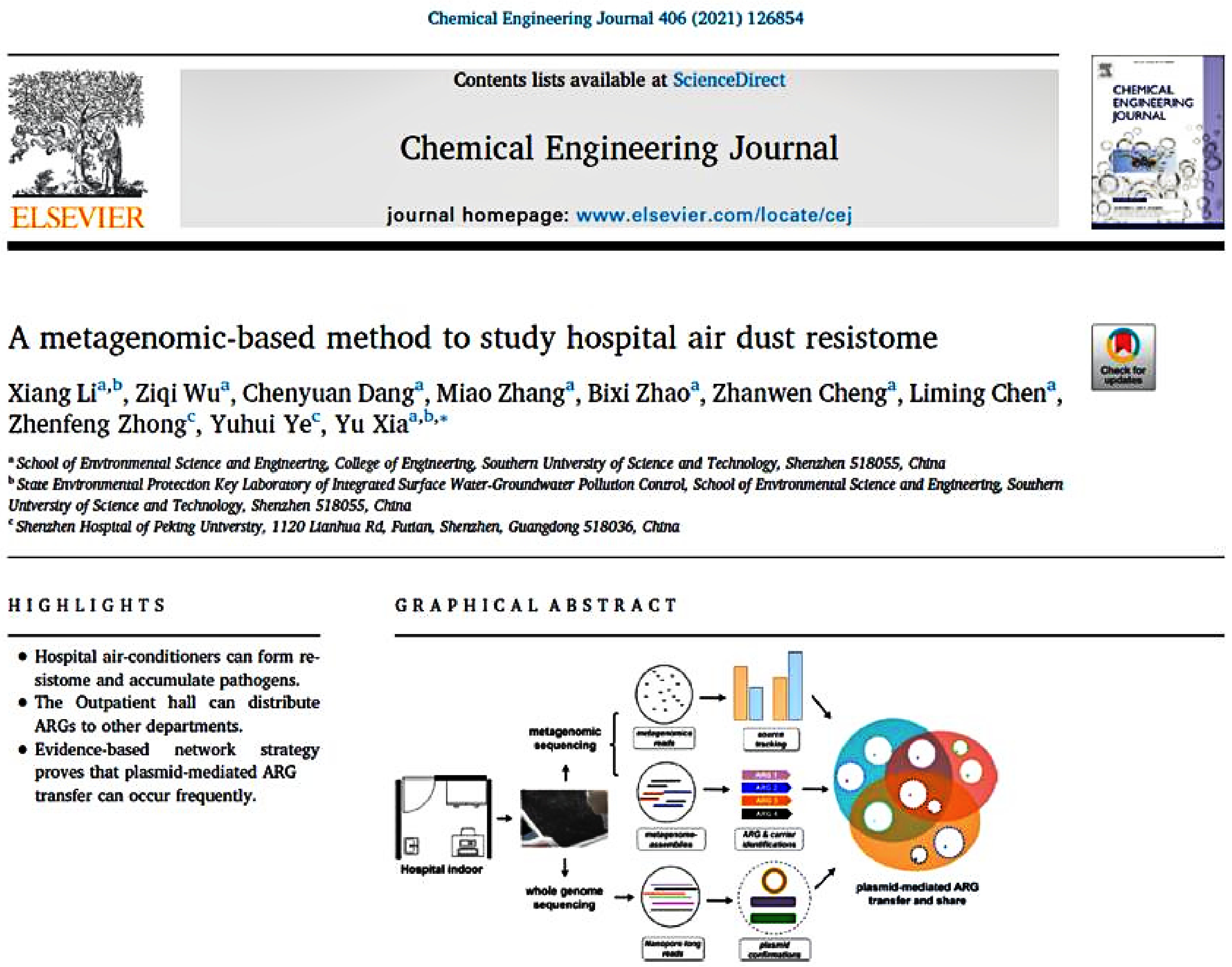
Yuhui Ye, MD, Chief Physician, Shenzhen Hospital of Peking University, Guangdong, China

LITTLE IS KNOWN ABOUT THE HOSPITAL INDOOR AIR SPREAD OF ARGS

Humans are closely tethered to the indoor environments, and they have become the most intimate ecosystem for humans nowadays. Lax et al. performed lots of indoor micro-ecology related sequencing work[2,3], and they revealed that human microbiota can influence indoor microbial communities and also be shaped by a built-in environment. Because hospital-acquired infections, HAIs, are being considered as the main reason for patients' deaths[3], the hospital micro-ecology research is drawing more attention. Currently, lots of effort have been made towards learning how microorganisms colonize and migrate in the hospital's indoor environment, and researchers have already identified the dominant hospital-associated pathogens (HAPs) and summarized their putative routes of transmissions, however, little is known about the possible indoor air ARG transmission route.

SAMPLING AND METAGENOMIC-BASED METHOD

As shown in Figure 1 (abstract art), both the Illumina metagenomic sequencing and ONT bacterial whole genome sequencing were included in our metagenom-


Chemical Engineering Journal 406 (2021) 126854

Contents lists available at ScienceDirect

Chemical Engineering Journal

journal homepage: www.elsevier.com/locate/cej

ELSEVIER

A metagenomic-based method to study hospital air dust resistome

Xiang Li[a,b], Ziqi Wu[a], Chenyuan Dang[a], Miao Zhang[a], Bixi Zhao[a], Zhanwen Cheng[a], Liming Chen[a], Zhenfeng Zhong[c], Yuhui Ye[c], Yu Xia[a,b,*]

[a] School of Environmental Science and Engineering, College of Engineering, Southern University of Science and Technology, Shenzhen 518055, China
[b] State Environmental Protection Key Laboratory of Integrated Surface Water-Groundwater Pollution Control, School of Environmental Science and Engineering, Southern University of Science and Technology, Shenzhen 518055, China
[c] Shenzhen Hospital of Peking University, 1120 Lianhua Rd, Futian, Shenzhen, Guangdong 518036, China

HIGHLIGHTS

- Hospital air-conditioners can form resistome and accumulate pathogens.
- The Outpatient hall can distribute ARGs to other departments.
- Evidence-based network strategy proves that plasmid-mediated ARG transfer can occur frequently.

GRAPHICAL ABSTRACT

Figure 1. A metagenomic-based method to study hospital air dust resistome (Chemical Engineering Journal 406 (2021) 126854 1).

ic-based approach. According to the hospital cleaning practice, windows are closed in summer but are regularly open during winter seasons due to the climate characteristics in Shenzhen city. Therefore, we performed sample collections in summer and winter, respectively.

We chose the Outpatient hall, the Ophthalmology, and the Pediatrics department as sampling locations, and the corresponding air dust samples were collected. In brief, we firstly collected the air-conditioner strainers and washed the dirt into the sterilized autoclavable containers using sterilized ddH2O. Thereafter, the "water samples" were filtered immediately using 0.22μm-sized filters. The filters were then used for DNA extraction.

Lastly, we used the Illumina HiseqXten-PE150 platform to perform metagenomics sequencing, and the bacterial whole genomes were sequenced using the GridION X5 platform (Nanopore sequencing technology) on R9.4 flowcell for 48 hours. In our data analysis approach, we applied ARGs-OAP v2.0 to characterize and quantify ARGs[4]. Besides, the sequencing reads were assembled using CLC Genomics Workbench 12 (Qiagen Bioinformatics, USA) according to different department clusters. We then predicted open read frames (ORFs) in each assembly by MetaGeneMark[5] software and applied Diamond to match these ORFs to the RefSeq protein database. MEGAN5[6] was used to parse the Diamond outputs, and the corresponding taxonomic annotations were used to search the ARG carrying bacteria.

AIR DUST RESISTOME CHARACTERISTICS

The Pediatrics summer sampling had 167 ARG detections, followed by 144 in the Outpatient hall, and only 42 in the Ophthalmology department. However, the Pediatrics winter had 384 ARG detections followed by the Ophthalmology and the Outpatient hall with 357 and 344, respectively.

Moreover, we detected 86 ARGs in winter but only 11 occurred in summer. The average normalized ARG concentration in summer was 0.0000257, 0.000761, and 0.000132 copies per 16S rRNA gene for the Outpatient hall, the Pediatrics, and the Ophthalmology, respectively; and the corresponding values changed to 0.000522, 0.000536, and 0.000524 in winter.

Overall, the air dust resistome exhibited an average of 0.00042 copies per 16S rRNA gene, which was less than the wastewater influent samples. *Acinetobacter*, Bacteroides, *Escherichia*, and *Staphylococcus* ARG carriers were mainly found at the Outpatient hall, but *Spirochaeta*, *Xanthobacter*, *Pseudomonas*, *Pseudoalteromonas*, and *Legionella* carried ARGs at the Ophthalmology and the Pediatrics department (Figure 2). Notably, *Pseudomonas* exhibited the most abundant aminoglycoside resistome at the Ophthalmology winter sample, and the Outpatient hall summer exhibited the highest tetracycline abundance. Our findings were consistent with some other studies since *Pseudomonas* was found to be the most frequently detected airborne bacteria in Taiwan ICUs[7], and the researchers from Iran concluded the beta-lactam resistant *Acinetobacter* and *Staphylococcus* were dominantly present in the hospital indoor air[8].

PLASMID-MEDIATED ARG TRANSFER

Unlike statistical association network method[9], we focused on an evidence-based strategy to establish network edges (Figure 2). Our evidence-based method applied strict cutoffs (over 99% similarity cutoff). In summary, *Micrococcus*, *Streptococcus*, *Staphylococcus*, and *Enterococcus* were identified in the Outpatient hall, showing the largest ARG genotype sharings. Notably, *Staphylococcus* carried 14 ARG genotypes, and the Ophthalmology and the Pediatrics departments exhibited fewer genera. In our study site, we found the ARGs against Aminoglycoside, bacitracin, β-lactam, chloramphenicol, macrolide, lincosamide, and streptogramin (MLS), multidrug, tetracycline, etc. aadD, CE, tetK, tetA, tetZ, and norA were the most commonly shared ARG genotypes among different departments. We have confirmed that the sharing of *Staphylococcus* tetK among different departments indeed happened using Nanopore sequencing technology. Additionally, plasmid-mediated CE transfer was observed between *Staphylococcus* and Corynebacterium in the Outpatient hall. Using our method, we successfully assembled 5 bacterial genomes, and we have noticed plasmid fragments, indicating plasmid transferring is highly possible. As shown in Figure 2, the movement of *Staphylococcus saprophyticus* plasmid among departments might be important for ARG and HAP transfer patterns in the studied hospital.

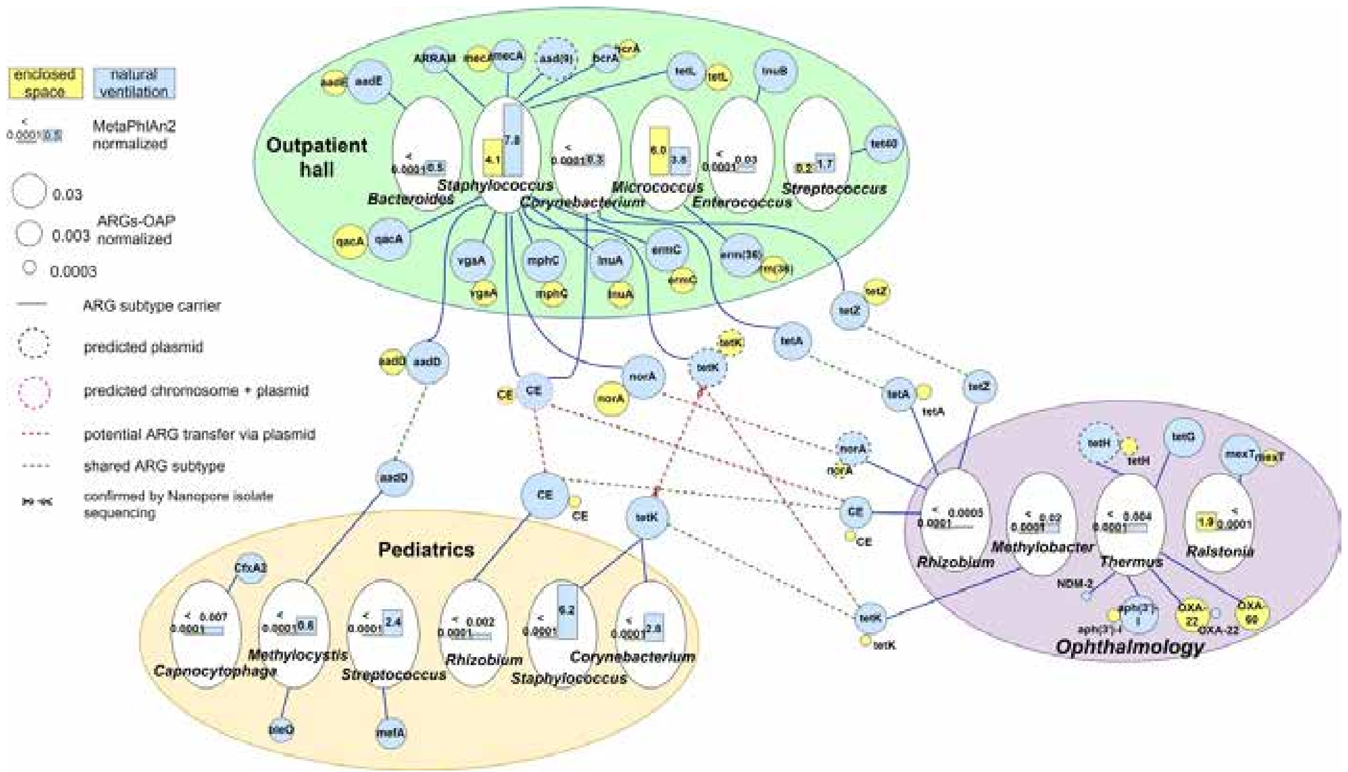


Figure 2 ARG genotype sharing network[1]. The ARGs that are drawn outsides of the departments represent the potential ARGs shared by airborne spreading (blue and yellow encode the ARGs that are identified under different airflow conditions).

NOTICES OF BEST MANAGEMENT PRACTICE TO ALLEVIATE ARG POLLUTION IN HOSPITAL

Some research groups modeled the microorganism concentrations with human occupancy, visiting patients among departments, indoor temperature, etc.[3,7], but the results only showed weak correlations. Since our study site is highly compacted and intensively used every day, this "weak correlation" may still cause big problems in our case. Besides, as discovered by Kotay et al.[10], the splashed droplets in washing sinks could lead to the ARG transmission in the hospital. Therefore, we believe that determining cleaning strategies based on specific bacterial carriers and applying appropriate cleaning management practices are essential to controlling ARG transmissions.

Meanwhile, some other practices, such as establishing anteroom inside of patients' rooms seem to work greatly[11]. Researchers also recommended providing positive air pressure to reduce pathogenic transmissions as they found humidity and outdoor air fractions had strong temporal patterns and strong correlations between rooms, which was also confirmed in this study. Notably, we have also detected almost the same amount of eukaryotic resistances in the studied hospital; however, the cleaning experts barely take special actions to inhibit eukaryotes. Therefore, the overlooked eukaryotic resistance should arise our concerns and a deeper understanding of eukaryotic resistance is much needed[12].

Dr. Yu XIA, PI of the Environmental Microbiology and Ecogenomics Laboratory at School of Environmental Science and Engineering, Southern University of Science and Technology (SUSTech), Shenzhen, China. Dr. Yu XIA got her PhD in Environmental Microbiology from The University of Hong Kong. She is interested in applying advanced sequencing and molecular technology such as long-read based metagenomics, microfluidics, and single-cell to explore the functionality of the unculturable majority of the environmental microbiome in engineered systems, indoor environments, and extreme environments.

Dr. Xiang LI is a faculty member at School of Environmental Science and Engineering, SUSTech, Shenzhen, China. Dr. Li obtained his PhD from West Virginia University, majoring in environmental engineering. His research interests include microbial source tracking in environmental waters, metagenomic sequencing, and microbial ecology.

Dr. Yuhui YE is the chief physician of the communicable diseases control department at Shenzhen Hospital of Peking University. Dr. YE has been working in communicable disease control and the corresponding management practice after joining in the hospital. Meanwhile, Dr. YE participates in the epidemiological investigation, disease control, and environmental monitoring work in Shenzhen City.

References

(1) Li, X.; Wu, Z.; Dang, C.; Zhang, M.; Zhao, B.; Cheng, Z.; Chen, L.; Zhong, Z.; Ye, Y.; Xia, Y. A Metagenomic-Based Method to Study Hospital Air Dust Resistome. Chem. Eng. J. 2021, 406, 126854. https://doi.org/10.1016/j.cej.2020.126854.

(2) Lax, S.; Smith, D. P.; Hampton-Marcell, J.; Owens, S. M.; Handley, K. M.; Scott, N. M.; Gibbons, S. M.; Larsen, P.; Shogan, B. D.; Weiss, S.; et al. Longitudinal Analysis of Microbial Interaction between Humans and the Indoor Environment. Science 2014, 345 (6200), 1048–1052. https://doi.org/10.1126/science.1254529.

(3) Lax, S.; Gilbert, J. A. Hospital-Associated Microbiota and Implications for Nosocomial Infections. Trends Mol. Med. 2015, 21 (7), 427–432. https://doi.org/10.1016/j.molmed.2015.03.005.

(4) Yin, X.; Jiang, X.-T.; Chai, B.; Li, L.; Yang, Y.; Cole, J. R.; Tiedje, J. M.; Zhang, T. ARGs-OAP v2.0 with an Expanded SARG Database and Hidden Markov Models for Enhancement Characterization and Quantification of Antibiotic Resistance Genes in Environmental Metagenomes. Bioinformatics 2018, 34

(5) Zhu, W.; Lomsadze, A.; Borodovsky, M. Ab Initio Gene Identification in Metagenomic Sequences. Nucleic Acids Res. 2010, 38 (12), e132. https://doi.org/10.1093/nar/gkq275.

(6) Huson, D. H.; Auch, A. F.; Qi, J.; Schuster, S. C. MEGAN Analysis of Metagenomic Data. Genome Res. 2007, 17 (3), 377–386. https://doi.org/10.1101/gr.5969107.

(7) Ping-Yun Huang, Zhi-Yuan Shi, Chi-Hao Chen, Walter Den, Hui-Mei Huang, J.-J. T. Airborne and Surface-Bound Microbial Contamination in Two Intensive Care Units of a Medical Center in Central Taiwan. Aerosol Air Qual. Res. 2013, 13, 1060–1069.

(8) Mirhoseini, S. H.; Nikaeen, M.; Shamsizadeh, Z.; Khanahmad, H. Hospital Air: A Potential Route for Transmission of Infections Caused by Beta-Lactam-Resistant Bacteria. Am. J. Infect. Control 2016, 44 (8), 898–904. https://doi.org/10.1016/j.ajic.2016.01.041.

(9) Li, B.; Yang, Y.; Ma, L.; Ju, F.; Guo, F.; Tiedje, J. M.; Zhang, T. Metagenomic and Network Analysis Reveal Wide Distribution and Co-Occurrence of Environmental Antibiotic Resistance Genes. ISME J. 2015, 9 (11), 2490–2502. https://doi.org/10.1038/ismej.2015.59.

(10) Kotay, S. M.; Donlan, R. M.; Ganim, C.; Barry, K.; Christensen, B. E.; Mathers, A. J. Droplet - Rather than Aerosol-Mediated Dispersion Is the Primary Mechanism of Bacterial Transmission from Contaminated Hand-Washing Sink Traps. Appl. Environ. Microbiol. 2019, 85 (2). https://doi.org/10.1128/AEM.01997-18.

(11) Araujo, R.; Cabral, J. P.; Rodrigues, A. G. Air Filtration Systems and Restrictive Access Conditions Improve Indoor Air Quality in Clinical Units: Penicillium as a General Indicator of Hospital Indoor Fungal Levels. Am. J. Infect. Control 2008, 36 (2), 129–134. https://doi.org/10.1016/j.ajic.2007.02.001.

(12) West, P. T.; Probst, A. J.; Grigoriev, I. V; Thomas, B. C.; Banfield, J. F. Genome-Reconstruction for Eukaryotes from Complex Natural Microbial Communities. Genome Res. 2018, 28 (4), 569–580. https://doi.org/10.1101/gr.228429.117.

PATIENT SAFETY & IPC ARE INTERDEPENDENT: NONE CAN WORK WITHOUT FULFILLING THE OTHER,

(WITH PARTICULAR EMPHASIS ON AMR AND COVID-19)

Abstract

Patient Safety is defined as the absence of preventable harm during care provision and the reduction of risk associated to harm to a minimum leve[1]. Infection Prevention and Control (IPC) is defined as the scientific approach and practical solution designed to prevent harm caused by infection to patients and health workers[(2)]. In other words, while Patient Safety focuses on the elimination of ALL preventable harms in healthcare, IPC focuses on the elimination of a specific preventable harm in healthcare, which is infection caused by healthcare practices, commonly named Healthcare Associated Infections (HAIs).

Patient safety is a significant challenge for healthcare systems globally. While, over the past 20 years, High Income Countries (HICs) and Low and Middle-Income Countries (LMICs), have put in place efforts to reduce patient harm, the problem persists, with harm being inflicted and lives continuing to be lost. Unsafe practices that harm patients lead to 64 million disability-adjusted life years (DALYs) lost and are one of the ten leading causes of death and disability globally[(3,4,5)]. This is more than the lives lost due to Tuberculosis and Malaria combined.

In addition to the negative medical consequences of unsafe care, there is also a significant economic impact on countries. The overall estimate is that, on average, 15% of the cost of health care expenditure and activity is attributed to harm across OECD countries[(6)].

While unsafe care is a global challenge for all healthcare systems, the problem is more pronounced in LMICs, where it is estimated that 2.6 million patients die each year due to unsafe care and approximately 75% of all global DALYs are lost due to preventable harm[(7)].

> “*Over the past two decades, there has been a major progress in our understandings of the above three challenges, namely: Patient Safety, Infection Prevention and Control -IPC, and AMR. It is safe to say that a major proportion has been bridged in the knowledge gap on Patient Safety, IPC, and AMR. Unfortunately, the same cannot be said about the implementation gap of these conditions.*”

Dr Abdulelah Alhawsawi, Director General, Saudi Patient Safety Center, Kingdom of Saudi Arabia, and Executive Committee Member, Global Sepsis Alliance
Mawahib Wang, Chief Nursing Officer, Health Services Ministry of Defense, Riyadh, KSA
Sofia Macedo, Manager for Capacity Building, Saudi Patient Safety Center, Riyadh, KSA

Unsafe care covers a number of areas: healthcare associated infections (HAIs), medication errors, adverse drug reactions, surgical errors, diagnostic errors, venous thrombo-embolism, pressure injuries, and patient falls to name a few. Health Care Associated Infections, HAIs, in particular, are responsible for the harm of hundreds of millions of patients worldwide every year[(8)] as a result of defective Infection Prevention Control, IPC, practices during the delivery of healthcare. It is estimated that, in

Europe alone, more than 2.6 million new cases of HAIs occur every year with a cumulative burden in DALYs being estimated to be higher than all other reported 32 communicable diseases[9,10].
Due to the magnitude and significance of HAIs, the World Health Organization's 1st Global Patient Safety Challenge in 2005 was introduced to address a major IPC cornerstone, namely Hand Hygiene: "The 5 HH Moments". The theme of the global patient safety challenge was: "Clean Care is Safer Care". This important initiative also helped introduce the World Hand Hygiene Day which is celebrated every year on May 5th.

AMR is another major public health concern that is linked to both patient safety and IPC. Almost 100 years after Sir Alexander Fleming discovered Penicillin (1928) in London, many microbes have evolved to develop resistance to antimicrobial treatments. Currently, around 700,000 thousand people die annually from AMR[11]. According to a review conducted by a committee chaired by Jim O'Neill, it is estimated that, unless a major intervention is made to address this growing challenge, AMR will claim the lives of 10 million people annually by the year 2050. This will, potentially, translate in a reduction of 2% to 3.5% in Gross Domestic Product (GDP) costing the world up to 100 trillion USD[12].
Over the past two decades, there has been a major progress in our understandings of the above three challenges, namely: Patient Safety, IPC, and AMR. It is safe to say that a major proportion has been bridged in the knowledge gap on Patient Safety, IPC, and AMR.

Unfortunately, the same cannot be said about the implementation gap of these conditions. While we, for the most part, know what to do (Knowledge Gap is bridged), we seem to have difficulties in doing it (Implementation Gap). The global efforts to reduce the burden of patient harm have not achieved considerable change and safety measures implemented by high income countries have had limited impact or have not been shaped for successful implementation worldwide[13]. The numbers speak louder than words regarding this state of affairs:

- Unsafe care claims the lives of approximately 5 million people, (more than the 3.6 million lives lost due no-access to care) with consequently 224 million years of life lost (YLL); these figures relate to LMICs alone[14].
- AMR will claim the lives of 10 million patients annually by the year 2050.
- Sepsis claims 11 million lives annually (attributed to both poor IPC and AMR)
- Hand hygiene compliance rate is around 40 – 50%. This poor compliance is shocking given the fact that the number one cause of HAIs is poor compliance with Hand Hygiene.

If we want to bridge the implementation gap, we have to address the following five obstacles:

1- Healthcare Safety Culture:
When compared to High Reliability Organizations (HRO) industries such as aviation, nuclear, oil and gas, the healthcare industry presents itself with a great room for improvement regarding the assurance of a safety culture. Few years ago, these industries were not as safe as they are today. Having gone through safety related watershed moments, they have learnt valuable lessons and safety was transformed and today there is roughly 1 in a million chance of a person being harmed while travelling by an airplane compared to a 1 in 300 chance of a patient being harmed while receiving health care[3,13]. HRO industries have transformed their safety culture through leadership commitment and integrating safety in their day-to-day activities.

These are organizations that consistently accomplish its goals while operating in a complex environment where accidents might be expected to occur frequently but manages to avoid or seeks to minimize catastrophes. Industries with a perceived higher risk such as the aviation and nuclear industries have a much better safety record than health care[13].

One of the biggest and consistent outcomes of HRO is SAFETY. While industries like aviation, nuclear, oil and gas, managed to become HROs, healthcare continues to struggle and falls behind these industries when it comes to safety! One does not need to look far to realize the safety challenges that both patients and healthcare workers are facing on a regular basis, especially nowadays during a pandemic like COVID-19.

If we are to transform safety culture in healthcare and move it, as a system, closer to becoming an HRO, we have to move away from addressing safety of patients and healthcare workers, separately, and start dealing with them as 'two sides of the same coin'. Knowing that the strengthening and resilience of healthcare systems, are paramount to achieving the Sustained Development Goal (SDG[3]), the only way we can succeed in reaching meaningful Universal Health Coverage (UHC) and SDG[3] is through introducing a new concept of safety, namely: Healthcare Safety that includes the following:
- Patient Safety
- HCW Safety
- Healthcare Facility Safety

2- Information Asymmetry:
In healthcare, there is a major gap between the knowledge and information that healthcare providers have compared to patients and their family. Such information asymmetry is potentially problematic and would negatively impact quality, safety, and patient experience, while at the same time increases cost.
The most impactful solution that closes this gap is the meaningful and practical empowerment strategies for patients and their families towards a sustainable person-centered approach to healthcare provision.

3- Lack of Resilience:
While the implementation of human factors engineering (HFE) and ergonomics in healthcare is still sporadic, HRO industries have integrated HFE in their entire processes and activities which created resilience, efficiency, as well as transformed safety.

4- Lack of Global Advocacy:
While Patient Safety, IPC, and AMR are very important public health challenges, the understanding of these conditions by the public and society in general is still weak. This is clear when one compares the level of public awareness towards the above global health concerns and the level of awareness and advocacy towards global climate change.
The only way to improve the public awareness about these important global public health problems is through a robust global advocacy. These issues have to move from being the concern of few interested researchers and experts into the mainstream of both public, clinicians, and global societal and political forces.

5- Lack of Collective Learning and Sharing:
One of the major challenges in ensuring patient safety is the absence of a global platform for reporting and learning from adverse events. Industries like aviation and nuclear have robust reporting and learning practices where the overall industry benefits from the safety alerts generated from any part of the world. For healthcare to be able to have such collective learning platform, we need to be speaking the same language. It is time to have a standardized taxonomy for adverse events similar to the standardized taxonomy for diseases namely, International Classification of Diseases (ICD). Such classification can be named International Classification of Adverse Events (ICAE) which could be introduced and endorsed by the WHO, the same way ICD was endorsed.

Another major challenge in healthcare, which is part of the reason behind writing this book, is the silos and fragmentation that characterize not only the practice of patient safety but the healthcare industry overall.

The authors hope that by now, one agrees that Patient Safety, IPC, Sepsis, and AMR are facets of the same complex multi-faceted healthcare system. While Patient Safety is the absence of ALL harm, and IPC is the absence of HAIs harm, in some part caused by AMR, we still refer to them as three separate entities. In most organizations, Patient Safety and IPC have two siloed different departments, and may or may not report to the same person in the C-suite. To add more silos and complexity, even a closely related issues like Sepsis and AMR are also addressed separately by, most of the time, two different departments.

Moreover, since nurses and midwives account for nearly 50% of global health workforce[15], investment in training this segment can cut cost and safe lives. The WHO stated in its 2020 report that nurses and midwives are critical for infection prevention and control, and increased nurse staffing levels and education in skill-mix teams correlate with reduced adverse events to hospitalized patients, including catheter-associated urinary infections, bloodstream infections, and ventilator-associated pneumonia[16].
All of these HAIs have high rate of morbidity and mortality and cost healthcare organizations millions of dollars every year. Many of these can be prevented or reduced by training nurses and midwives on best practices and proper hand hygiene, considering that poor hand hygiene is responsible for 40% of infections transmitted in hospitals[17].
Lessons like the ones learned from the Massachusetts Nursing Home Project need to be utilized in coming up with new guidelines and policies to improve delivery of healthcare and IPC practices in nursing homes. Just like other parts of the United States Massachusetts nursing homes were hit hard with COVID-19 and many residents lost their lives.

In response, a $130 million fund was allocated by Governor Charles Baker to fund new measures and protocols to do mandatory testing of all residents and staff and implement a 28-point infection control list[18]. This was also supported by comprehensive training and education of nursing home's staff across the state. The result was successful control of the wide spread of COVID-19 in nursing homes in the state. This approach if replicated in all other nursing homes around the world can prevent spread of infections in the future. If we want to transform healthcare and achieve the Quadruple Aim: Better Health, Better Care, Lower Cost, and Satisfied Healthcare Workers, it is time that we break down the silos in healthcare and redesign our care delivery processes in an agile and efficient way.

Dr. Abdulelah Alhawsawi is the founding Director General of the Saudi Patient Safety Center, which is 1 of only 5 WHO collaborative center worldwide, and MOH Advisor on Patient Safety. He holds a Dual Certified Boards (American -Canadian) of general surgery with sub-specialty in Transplant and Hepatobiliary Surgery. He is a consultant to several national and international quality and safety organizations and recently became an executive committee member of the Global Sepsis Alliance (GSA). He was part of the Expert Panel on the 3rd Global Patient Safety Challenge of the WHO and chaired the Organizing Committee for the 4th Global Ministerial Summit on Patient Safety in Jeddah, Saudi Arabia in 2019. Dr. Alhawsawi has helped introduce Patient Safety as a G20 priority in the 2020 G20 of Saudi Arabia. Currently, Dr. Alhawsawi is part of the WHO's Global Patient Safety Action Plan Taskforce.

Ms. Mawahib Wang is the Chief Nursing Officer of Armed Forces Hospitals for the Ministry of Defense. She graduated from University of Texas Health Science Center with a Bachelor of Nursing and obtained her Master degree in Healthcare Management from Walden University. She has extensive experience in critical care nursing and managerial leadership in the USA then in Saudi Arabia. She started the first comprehensive simulation training center in Security Forces hospital. She has accreditation post graduate diplomas in both Midwifery and Critical Care in the military hospital. She introduced the Magnet recognition program for King Fahad Specialist Hospital. Her role expanded to be the Chief Nursing Officer for the first cluster hospitals in the Ministry of Health and lead the transformation program 2030 for nursing.

Sofia Macedo is the Capacity Building Manager for the Saudi Patient Safety Center, Ministry of Health, in Riyadh, Saudi Arabia. Portuguese citizen, with a degree in the Science of Nursing, from Oporto Nursing School in Portugal, she has spent most of her professional career abroad and carries 15 years of international and national clinical practice and 11 years of expertise within the Saudi healthcare system. Sofia has an MSc in Evidence Based Healthcare from the University College of London; UK. With expertise in clinical education & research, quality, Magnet Fundamentals and Patient Safety, she leads the planning and curriculum development on Patient Safety at national level. She was in the Health File team of the 2020 G20 Summit in Saudi Arabia.

References

(1) World Health Organization. Retrieved October 7, 2020, from https://www.who.int/patientsafety/en/

(2) World Health Organization. Retrieved October 7, 2020, from https://www.who.int/infection-prevention/about/ipc/en/

(3) World Health Organization. The top 10 causes of death [Internet]. Geneva, Switzerland; 2018 May. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

(4) Global action on patient safety. World Health Organization. Executive Board: 144th session. EB144/29. 12 December 2018.

(5) National Academies of Sciences, Engineering, and Medicine. Crossing the global quality chasm: Improving health care worldwide. Washington (DC): The National Academies Press; 2018

(6) Slawomirski L, Auraaen A, Klazinga NS. The economics of patient safety. 2017 Jun 26 [cited 2019 Jul 25]; Available from: https://www.oecd-ilibrary.org/ social-issues-migration-health/the-economics-ofpatient-safety_5a9858cd-en;jsessionid=cBxjfNhlIC4ZhfHkDy1pvCr. hfcHkDy1pvCr

(7) Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ Qual Saf. 2013 Oct 1;22(10):809–15

(8) WHO. Report on the burden of endemic health-care-associated infection worldwide. World Health Organization, Geneva 2011 http://www.who.int/infection-prevention/publications/burden_hcai/en/

(9) Cassini A Plachouras D Eckmanns T et al. Burden of six healthcare-associated infections on European population health: estimating incidence-based disability-adjusted life years through a population prevalence-based modelling study. PLoS Med. 2016; 13: e1002150

(10) Allegranzi B, Kilpatrick C, Storr J, Kelley E, Park BJ, Donaldson L, et al. Global infection prevention and control priorities 2018–22: a call for action. Lancet. Global health, 2017, 5:12, e1178-e1180.

(11) World Health Organization. New report calls for urgent action to avert antimicrobial resistance crisis. April 2019. Retrieved October 7, 2020, from https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis.

(12) O'Neill J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. UK Parliament. December 2014. Retrieved October 7, from https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20a%crisis %20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

(13) Macedo MS, Mandourah Y., Moore A., AlHawsawi A. 1999–2019: Twenty years of watershed moments for patient safety. Saudi Critical Care Journal. 2019. Vol. 3 (1). Page3-11.

(14) Kruk ME et al. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. Lancet 2018; 392: 2203–12. DOI:https://doi.org/10.1016/S0140-6736(18)31668-4

(15) World Health Organization. Health Workforce (Internet). Geneva, Switzerland; Available from: https://www.who.int/hrh/nursing_midwifery/nursing-midwifery/en/

(16) World Health Organization. Nurses and midwives critical for infection prevention and control (internet). Geneva, Switzerland; Available from: https://www.who.int/infection-prevention/tools/core-components/CCs-and-MinReq.pdf?ua=1

(17) Angela Revelas, Healthcare – associated infections: A public health problem. Niger Med J. 2012 Apr-Jun; 53(2): 59–64. doi: 10.4103/0300-1652.103543

(18) Lipsitz L, Lujan A, Dufour A, Abrahams G, Magliozzi H, Herndon L, Dar M. Stemming the Tide of COVID-19 Infections in Massachusetts Nursing Homes. Journal of the American Geriatrics Society, 2020; DOI: 10.1111/jgs.16832

COVID-19 TODAY & AMR TOMORROW : ECONOMIC IMPACT & POLICY GLOBAL HEALTH SECURITY

SECTION V

THE UNEVEN ECONOMIC EFFECTS OF COVID-19

> *If this argument is correct, it follows that the economic consequences of COVID-19 are likely to remain most severe in the most advanced, post-industrial, financialized countries of the world, notably the US and the UK, while economic recovery in Asia proceeds along lines that are far closer to normal*

James K. Galbraith, Lloyd M. Bentsen Jr. Chair in Government/Business Relations and Professor of Government, The University of Texas, Austin, USA

COVID-19 is an equal-opportunity threat for all of humanity, yet its economic effects are curiously uneven, and in ways that may seem surprising at first. Europe (including the UK) and the United States have been hit hard, with second waves surging in parts of both continents, and with deep and so far intractable economic recessions. China, Korea, Vietnam, and Taiwan have the epidemic under control, with life returning largely to normal, even in Wuhan, the original epicenter of the outbreak. Although evidence is spottier, some of the world's poorer countries seem to have fared better than some of the wealthiest, though not as well as those in the middle-income strata of eastern Asia.

What accounts for this pattern? Simple ideological differences cannot, as some of the Asian countries are ostensibly socialist, others ostensibly capitalist, some ostensibly democratic and others not, and all of them in practice a blend of models that defy easy ideological characterization. And while it is tempting in a political season to lay the blame in the US and UK on defective national leadership, in fact both countries have competent public agencies and, in the US case, state and local governments that held lead responsibility for public health and that could and did take matters into their own hands.

But in any event, the economic consequences of the pandemic were and are only in part a result of qualities or defects in the immediate approach to public health. They must also depend on the resilience of the economies – just when you drop a vase, whether it breaks depends partly on how far it falls, and partly on what the vase is made of. And here we run into an economic question.

For most economists, the underlying economies are essentially alike: they all have businesses, households, governments, producers and consumers, and the textbook models that apply to them are essentially universal. There are two major mainstream variations on this view:

- the neoclassical or neoliberal view of the economy as a self-regulating structure, which sees the pandemic as a shock that will be reversed by natural processes of self-stabilization once the virus is controlled. This view, which is very much that of the incumbent administration in the United States, appears to be shared by the ordo-liberal factions still dominant in Europe. It accepts that the pandemic will continue for a time, is prepared to tolerate it so long as health care facilities are not overwhelmed by an influx of severe cases, and counts on the belief that in due course a therapy or a vaccine will become available. When that happens, in this view, the economic problems will resolve on their own, as people will return quickly to their past patterns of consumer behavior, and ultimately business investment.

- The neo-Keynesian view, which differs from the neoliberal in only one significant respect, namely a belief that rigid wages and prices (or asymmetries of information) ordinarily prevent the market adjustments that would otherwise occur. Thus a failure of prices and wages to adjust to lower levels of demand risks a prolonged recession. But in this view the problem can be resolved by infusions of cash, known as "stimulus," measures that "prime the pump" or "kick-start the engine" of renewed prosperity. "Give them money and they will spend" is the neo-Keynesian mantra. Among many things the neo-Keynesians share with the neoliberals is a belief in the unlimited desire of consumers for more goods and services, and a failure to distinguish, as ordinary consumers invariably do, between what is necessary and what can be forgone without major loss. Neither school has ever absorbed the reality of the affluent society, nor has it understood the role played by debt and credit in the finances of the modern Western (and especially American) middle class.

My argument starts from a proposition in classical economics, well stated by Adam Smith, that a large market entails a division of labor. In an integrated world economy, countries and regions are differentiated from each other, hold differing positions in a hierarchy of production and wealth, and they occasionally struggle with each other to climb to a higher position – or to avoid sinking to a lower one. This structural differentiation is the key to understanding why COVID-19 has a different economic effect in different places. I will try here to sketch the contrast especially between Asia, on one side, and the United States, United Kingdom and Europe on the other.

Taking the case of the United States, we observe that over 50 years the country has evolved from a dominant industrial and manufacturing power to an economy with a dual structure. On one side the leading sectors are technology and finance; on the other, American employers are a vast complex of service providers, a sector where real wages are maintained by cheap imports, the strong dollar, and quality advances in consumer goods, and by an elastic supply of credit to cover the costs of higher education, housing and health care.

Further, as a consequence of having been the world's leading affluent society on a continent with abundant land, American families tend to be house-rich; they live in their own spaces, with kitchens, bathrooms and backyards complete.
Each of these elements of the US position has proved a serious economic disadvantage in the face of the pandemic.

- The global market for advanced capital goods has declined nearly to the point of collapse, and national policies cannot revive it. Aircraft are a leading example: they will be built only so long as they can be sold, and airlines will buy them only when they need to, which is not the case so long as travellers world-wide have chosen not to fly. In the oil industry, the US has a high-cost domestic sector whose fate rests on the world price; national policy is again helpless if new wells cannot be dug at a profit. Commercial construction will not revive while office buildings and malls are empty. These factors all feed back on to the health of the banks, though how and when the financial strains will be exposed is anyone's guess.

- The US services sector provides, to an amazing degree, the pleasures and diversions of a wealthy society, in restaurants, bars, spas, coffee-houses, resorts, casinos, music festivals, gyms, nail and hair salons, massage therapists and tattoo artists – activities that animate economic life but are in no way essential. And yet, when they collapse they take with them the incomes that are essential to the economic machine, for it is the spending on other services of those who provide services that makes the merry-go-round turn. But public health and economic anxiety can and have brought the merry-go-round to a halt. To protect their health and their homes, middle-income Americans retreat to the relative safety of their homes, leaving the working poor, who live in close quarters and work in essential sectors such as food distribution and health care, to shoulder the brunt of the infections.

- And the third problem is that when incomes fail, debt contracts continue to apply, so that Americans are exposed to evictions, foreclosures, liquidations, utility stoppages and their neighborhood effects, notably blight and declining property values, which compound difficulties even for the solvent. The problem of debts can be deferred, through forbearance on evictions and foreclosures. But eventually it will have to be faced, somehow, and the entire structure of American wealth-holding, based as it is on private credit and private debt, will come into question when that happens.

THE BROAD CONTRAST WITH THE ASIAN ECONOMIES CAN BE SEEN ON ALL THREE ISSUES

- In China, Korea, Vietnam, or Taiwan and elsewhere in Asia with the partial exception of Japan, the economic center of gravity lies in the manufacture of consumers' goods, from shoes and clothing to appliances and electronics – for which demand is far more stable, more closely related to national income, and amenable to being supported by Keynesian measures of economic stimulus at the national level.

- In Asia the urban population lives mainly in apartments, in close quarters. And while this is a disadvantage from the standpoint of contagion, it also means that the service economy is more essential to daily life, and therefore more resilient when the public health issues are largely resolved. Asians cannot so easily retreat, as most Americans and many Europeans can, to the safe haven of a detached private home.

- Finally, deep and chronic indebtedness is less common, and less likely to lead to foreclosures and evictions, for social policy reasons. Further there is a strong urge in Asian society to save for education and health care, so these sectors are also substantially less financialized, and one does not read of an impending crisis of bankruptcies among the ordinary middle classes of China or Vietnam.

For these reasons, while the Asian societies faced a potential public health disaster that required a draconian – and so far, largely effective – immediate response, once the virus was controlled economic activity could and did return quite quickly to levels approaching previous norms.

As for Europe, it would appear, the continent occupies an intermediate position on each count. It has a balance of capital and consumer goods industries, a culture of service provision that is relatively robust, and a degree of household financialization and detached-home suburbanization between the Asian and the American levels.

So while Europe (taken as a whole) has suffered from problems akin to those in America in dealing with the pandemic proper, namely decayed public health investment, shortages of protective equipment and a citizenry with varying willingness to cooperate with official mandates, one may reasonably expect that in due course the European economic revival will be somewhere between the Asian rebound and the American depression.
If this argument is correct, it follows that the economic consequences of COVID-19 are likely to remain most severe in the most advanced, post-industrial, financialized countries of the world, notably the US and the UK, while economic recovery in Asia proceeds along lines that are far closer to normal.
Correspondingly, effective policy in the advanced countries will require far more radical measures than political discourse presently contemplates. In particular, the advanced industries, energy sector and construction will all need to be restructured and reoriented to public purpose, in the manner of the New Deal (or the proposed Green New Deal), to deal with urgent needs including energy transformation, the redesign of urban living and climate change. Service industries will likewise require a new economic model, largely cooperative and nonprofit, to ensure that a private services sector can continue in existence under a general retrenchment of private purchasing power.

A public job guarantee will be necessary to reduce, and ultimately eliminate, the anxieties and excess savings propensities associated with fear of mass unemployment. And – perhaps most difficult and sure to provoke conflict – debts will need to be written off and the financial sector reorganized to suit.

Of course none of these measures are likely. Indeed the need for them has not yet been acknowledged by any influential voices in public discourse. So the prognosis for the advanced, globalized and financialized economies of the Anglosphere is poor, while that for Europe is uncertain.

It is therefore most likely, at the present time, that the economic result of the pandemic will accelerate the transfer of global economic leadership from the West to the rising powerhouses of Asia.

James K. Galbraith holds the Lloyd M. Bentsen Jr. Chair in Government/Business Relations at the Lyndon B. Johnson School of Public Affairs and a professorship in Government at The University of Texas at Austin. Galbraith holds degrees from Harvard University (BA) and Yale University (MA, M.Phil, PhD). He was Executive Director of the Joint Economic Committee of the United States Congress in the early 1980s and has advised the State Planning Commission of P.R. China and the Greek Finance Ministry. He chaired the board of Economists for Peace and Security from 1996 to 2016 (www.epsusa.org) and directs the University of Texas Inequality Project (http://utip.lbj.utexas.edu). He is a managing editor of Structural Change and Economic Dynamics. In 2010, he was elected to the Accademia Nazionale dei Lincei. In 2014 he was co-winner with Angus Deaton of the Leontief Prize for Advancing the Frontiers of Economics. In 2020 he received the Veblen-Commons Award of the Association for Evolutionary Economics.

James K. Galbraith's recent books include:

Welcome to the Poisoned Chalice: The Destruction of Greece and the Future of Europe (2016)

Inequality: What Everyone Needs to Know (2016)

The End of Normal: The Great Crisis and the Future of Growth (2014)

Inequality and Instability: A Study of the World Economy Just Before the Great Crisis (2012)

The Predator State: How Conservatives Abandoned the Free Market and Why Liberals Should Too (2008).

References

Recent COVID-19 articles/interviews:

https://www.project-syndicate.org/onpoint/why-america-is-miserable-by-james-k-galbraith-2020-09

https://theintercept.com/2020/09/01/biden-economic-policy-us-economy/

https://www.thenation.com/article/politics/democratic-platform-pandemic-plank/

https://www.socialeurope.eu/yes-someone-is-to-blame

https://www.project-syndicate.org/commentary/united-states-economy-illusions-of-reopening-by-james-k-galbraith-2020-06

https://nymag.com/intelligencer/2020/05/coronavirus-debt-forgiveness-rent-mortgage-recession.html

https://progressive.international/blueprint/8b29fc89-4ac5-4f16-aa82-848f354383dd-azmanova-galbraith-disaster-capitalism-or-the-green-new-deal/en and https://www.alternatives-economiques.fr/choix-entre-capitalisme-desastre-new-deal-ecologique/00092889

http://www.defenddemocracy.press/we-need-a-radically-different-model-to-tackle-the-covid-19-crisis-by-james-k-galbraith/
https://democracyjournal.org/magazine/the-pandemic-and-capitalism/

https://prospect.org/economy/bad-economic-theory-and-practice-demolished/

More at: https://tinyurl.com/y8k5fxc4
or https://lbj.utexas.edu/galbraith-james-k (scroll down)Inequality and Globalization:

https://p.feedblitz.com/t3.asp?/973841/8345800/7004323_/www.paecon.net/PAEReview/issue92/GalbraithChoi92.pdf

Inequality and US Presidential Elections:

https://www.sciencedirect.com/science/article/abs/pii/S0954349X19304047

Recent TV, Radio and Podcasts:

https://www.bbc.co.uk/programmes/w3csz7wz

https://theintercept.com/2020/09/17/deconstructed-galbraith-coronavirus-economic-crisis/

Henry Stewart Talks: https://hstalks.com/t/4303/government-response-and-economic-impact-during-cov/?business

Diem25 with Yanis Varoufakis: https://www.youtube.com/watch?v=tMURR7WSZvE&feature=youtu.be

https://www.shankerinstitute.org/event/higher-education-funding-impact-coronavirus

NHK Global Agenda: https://www3.nhk.or.jp/nhkworld/en/ondemand/video/2047053/

Festival Digit Justice Fiscale: https://www.youtube.com/watch?v=IxhKuHHPTsc&feature=youtu.be&app=desktop

LBJ in the Arena: https://lbj.utexas.edu/lbj-arena-fiscal-meltdown

France Culture: https://www.franceculture.fr/emissions/radiographies-du-coronavirus/james-k-galbraith-nous-sommes-face-a-une-crise-fondamentale-du-modele-capitaliste

More at: https://tinyurl.com/y8k5fxc4
or https://lbj.utexas.edu/galbraith-james-k (scroll down)

" THE SYDNEY STATEMENT ON GLOBAL HEALTH SECURITY "

Global Health Security 2022
International Convention Centre
Sydney 21 - 24 June 2022

In June 2019, over 800 members of the global health security community gathered in Sydney, Australia, to participate in the first International Scientific Conference on Global Health Security. Participants came from over 65 countries, representing academia, local, national and international governmental and non-governmental organizations, public and animal health and security professionals, and the private sector, all committed to advancing global health security. As a product of this conference, we present "The Sydney Statement on Global Health Security."

Global health security is a state of freedom from the scourge of infectious disease, irrespective of origin or source. It is achieved through the policies, programmes, and activities taken to prevent, detect, respond to, and recover from biological threats. There are numerous challenges that pose significant risk to global health security, including a wide array of pathogens that present an existing and ongoing threat to both individual and collective health, antimicrobial resistance (AMR) and the emergence of currently untreatable infections, the potential for deliberate use of a biological weapon, and the synthesis of eradicated or novel pathogens. The complexity of addressing these challenges is amplified by a multitude of contextual factors. These threats know no borders and have global consequences requiring more effective collective action.

Addressing global health security threats should be guided by the following set of principles:

1. Global health security interventions must strive to be inclusive, equitable, and data driven.

2. A minimum level of disease prevention, detection, and response capabilities are critical for all countries, as epidemics anywhere threaten the health of everyone. Achieving global health security is also intricately linked with efforts to achieve universal health coverage, efforts to strengthen other vital aspects of broader health and security systems, and the Sustainable Development Goals.

3. Governments must cooperate programmatically, organizationally and financially to foster compliance with the International Health Regulations and other associated legal and regulatory agreements to ensure effective global governance of public health emergencies, and in so doing, en-

courage international organisations and NGOs to maintain the integrity of international norms, respect for human rights, and social justice. Transparent discussion, sharing, and measurement of global health security capacities is vital for achieving this goal.

4. Achieving global health security requires individual, group, and systems decision making and activities that strengthens capacity across all levels of societal interaction and disciplines. Making the world a healthier, more equitable, and safer place requires action and engagement from all, including the philanthropic, public and the private sector.

5. Global health security must embrace a One Health approach, not only to prevent and respond to disease, but also to protect ecosystems that underpin human, animal, and environmental health. All relevant sectors must be meaningfully involved and engaged, including heath, agriculture, environmental, security, and other vital components.

6. Countries with higher capacity to respond to adverse public health events have a moral and ethical duty to work in partnership with those with lower capacity to strengthen their capabilities in a sustainable manner.

7. International partners and national governments must commit to sustainable, comprehensive funding mechanisms to support global health security. Long-term strategic thinking for global health security must be supported by a diverse, inclusive community of practice, committed to providing the best evidence possible to inform transparent decision making. Achieving global health security requires commitment to the above principles, and the institutional arrangements that advance them globally, to reduce infectious disease threats, including local empowerment, capacity building, data and benefits sharing, transparency, and accountability. Stronger health systems, Universal Health Coverage, and Health-In-All-Policies, from the local to the global levels are all dependent upon and supportive of global health security.

IMPROVING QUALITY & ACCESS TO CARE FROM INFECTIOUS TO NON-COMMUNICABLE DISEASES

SECTION VI

INTERNATIONAL COLLABORATION FOR AFFORDABLE AND EQUITABLE GLOBAL RADIOTHERAPY TREATMENT

> *Smart Technologies to Extend Lives with Linear Accelerators. STELLA, is a multidisciplinary effort that will produce a comprehensive medical linear accelerator-based RT treatment system for transformative treatment of patients with cancer in Low and Middle Income Countries and underserved areas in High Income Countries, while providing access to education and training to support building a sustainable workforce.*

Manjit Dosanjh, PhD, European Organization for Nuclear Research (CERN), Switzerland, and University of Oxford, UK, STELLA's Project Leader, and member ICEC Cancer.
C. Norman Coleman, MD, DSc (h.c.) FASTRO, FASCO, FACP, FACR Senior Medical Advisor, ICEC (https://www.iceccancer.org), Former Professor and Chair of Radiation Oncology, Harvard Medical School, USA

The annual global incidence of cancer is projected to rise in 2040 to 27.5 million cases (16.3 million deaths) with 70% occurring in LMICs where there is a severe shortfall in the availability of radiotherapy (RT) - an essential component of overall curative and palliative cancer care. Though over 50% of individuals diagnosed with cancer benefit from RT, access is often poor to non-existent in LMICs. Significant disparities exist between high and low-income settings, with 11.4 machines per million patients in North America versus 0.05 machines per million patients in Sub-Saharan Africa. Further, there are no machines in nearly forty countries worldwide, mostly in low-income countries, 27 of these are in Africa.

In recognition of this extreme shortfall of radiotherapy capacity in LMICs, the International Cancer Expert Corps (ICEC) sponsored, and the European Organization for Nuclear Research (CERN) hosted a workshop at CERN, in November 2016, to define the design characteristics of a novel medical linear accelerator (linac) for challenging environments. *https://indico.cern.ch/event/560969/overview.*

Three other workshops have followed involving medical and technical experts from CERN, the International Cancer Expert Corps (ICEC) and, since 2017, the UK Science and Technology Facilities Council (STFC) as well as representatives from ODA countries. This multidisciplinary collaboration has brought together world class specialists ranging from accelerator physicists, medical physicists, radiobiologists, radiation oncologists and radiotherapy technologists to the representatives from ODA countries in order to understand the challenges they face in delivering radiotherapy in those regions and to develop innovative solutions, especially for our partners across Africa. The 4th Conference to coordinate efforts to design and develop an affordable and robust yet technically sophisticated linear accelerator-based radiation therapy treatment (RTT) system was held in Gaborone, Botswana on March 20-22, 2019. *https://indico.cern.ch/event/767986/overview.*

This enables a significant number of physicians, physicists and staff from Sub-Sahara Africa and other LMICs to attend, present their reports and interact with the scientists working with them in their own region of the world thereby generating a sense of a global community working toward a common goal.

Smart Technologies to Extend Lives with Linear Accelerators (STELLA), is a multidisciplinary effort that will produce a comprehensive medical linear accelerator-based RT treatment system for transformative treatment of patients with cancer in LMICs and underserved areas in (HICs), while providing access to education and training to support building a sustainable workforce.

Map showing the variation in RT capacity across Africa that is especially pronounced in the Sub-Saharan region where most of the countries do not have RT machines

Manjit Dosanjh with Taofeeq Ige at a workshop on radiation therapy treatment systems in Gaborone, Botswana.

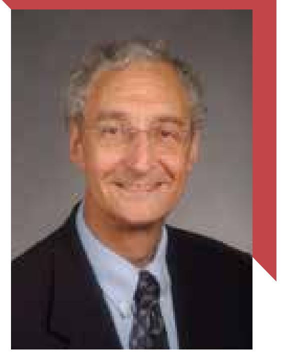
Dr Simeon Aruah, Abuja, Nigeria

Ideas on how to overcome the challenges from the grass-roots

Norman Coleman and Dr. Surbhi Grover discuss future plans for mentorship and innovative technology in Botswana.

Fourth workshop group photo in front of Avani Gaborone Hotel, March 2019 (all photos M. Dosanjh)

Manjit Dosanjh is the Project Leader for STELLA (Smart Technologies to Extend Lives with Linear Accelerators), honorary CERN Staff, the particle physics laboratory in Geneva, Switzerland and Visiting Professor at the University of Oxford. She holds a PhD in Biochemical Engineering from the UK and her professional efforts in the fields of biology and the medical applications of physics span more than 30 years, during which she has held positions in various academic and research institutions in Europe and the U.S., including the Massachusetts Institute of Technology, the Lawrence Berkeley National Laboratory at the University of California, the European Commission Joint Research Centre in Italy. Dosanjh joined CERN in 1999 where she has worked to apply technologies originally developed for particle physics to the domain of life sciences, aiming to translate and transfer knowledge about physics to society at large. She is also actively involved in helping non-profit health, science education and gender related organisations in Geneva.



Dr. Coleman is board certified in internal medicine, medical and radiation oncology. Following 7 years as a faculty member at Stanford he was Professor/Chairman of the Harvard Medical School Department of Radiation Oncology (1985-99). His work in ICEC is an Official Outside activity from his position as Associate Director of the NCI Radiation Research Program and Senior Medical Advisor in the Office of the Assistant Secretary for Preparedness and Response, DHHS, focused on radiological/nuclear disaster response. For this and for his work in Japan during the 2011 multiple disaster he received the 2011 Samuel J. Heyman, Service to America Homeland Security Medal. With a career-long interest in community outreach to the medically underserved, at NCI he helped conceptualize the Cancer Disparities Research Partnership program which demonstrated the success of mentoring in building cancer research programs in underserved regions. which illustrated the critical importance of sustainability and the need for NGO's.

EPIDEMIOLOGY OF CATHETER-ASSOCIATED URINARY TRACT INFECTIONS IN A MIDDLE EAST HOSPITAL

"Catheter-Associated Urinary Tract Infection (CAUTI) are often caused by antibiotic resistant bacteria, hence the importance of further research on epidemiology and prevention. "The risk of acquiring a CAUTI increases each day the urinary catheter remains in situ. In most cases, these urinary catheters are placed for inappropriate reasons and clinicians are often unaware that their patients have catheters." Effectively preventing CAUTI is part of Patient Safety against AMR"

Dr Shafi Mohammed, Director and co-Chair, Cleveland Clinic Infection Control Committee, Abu Dhabi, United Arab Emirates
Elias Tannous, MBA, Director, Arab Countries Infection Control Network, ACICNet, and Infection Control Specialist, Cleveland Clinic, Abu Dhabi, UAE
Dr Ahmad Nusair, Chair, the Infection Control Committee and Program Director of the Internal Medicine Residency, Cleveland Clinic, Abu Dhabi, UAE
Claire Nolan, nurse, Infection Control Department - Cleveland Clinic Abu Dhabi, United Arab Emirates

INTRODUCTION

Urinary tract infections (UTIs) are the fifth common type of healthcare-associated infections (HAIs) account for more than 9.5% HAIs reported in acute care hospitals (Magill et al, 2018).
Studies have shown that between 12 – 16% of hospitalized patients may receive short-term indwelling urinary catheters during their hospitalization, with about two third being inserted in intensive care patients (McGuckin, 2012; Lo et al, 2014).

The most frequent complication associated with CAUTI are prostatitis, epididymitis and orchitis in males, whereas others include cystitis, pyelonephritis, blood stream infections, endocarditis, vertebral osteomyelitis, septic arthritis, endophthalmitis and meningitis. Undoubtedly, these complications can cause discomfort to the patient, adding additional length of stay, costs and mortality (Scott, 2009). In the US, CAUTI claims an estimated 13,000 deaths annually (Kleven et al, 2007).

The risk of acquiring a catheter associated urinary tract infection (CAUTI) increases by 3 -7% for each day the urinary catheter remains in situ (NHSN, 2019). In most cases, these urinary catheters are placed for inappropriate reasons and clinicians are often unaware that their patients have catheters, leading to prolonged and unnecessary use and subsequent risk of infections (Munasinghe et al, 2001; Jain et al, 1995).

Reported rates of CAUTI among inpatients vary substantially. In the USA, the CAUTI rate in 2012 as reported to the National Healthcare Safety System (NHSN) was 0.5 -5.3/1,000 urinary catheter days on adult inpatient units and 1.2 – 5.0/1,000 urinary catheter days in the intensive care units (NHSN, 2019). Although morbidity and mortality from CAUTI is considered to be relatively low compared to other HAIs, the burden of urinary catheter use leads to a large cumulative incident of infections with resulting infectious complications and deaths (NHSN, 2019). On the other hand, while fewer than 5% of bacteriuric cases develop bacteremia, CAUTI is the leading cause of secondary nosocomial bloodstream infections and accounts for about 17% of hospital-acquired bacteremia with an associated mortality of approximately 10% (Saint, 2000). Evidence from epidemiological studies have shown that an estimated 17% to 69% of CAUTI may be preventable with recommended infection control measures; which translates up to 380,000 infections and 9000 deaths related to CAUTI per year could be prevented (CDC CAUTI guidelines).

The primary objective of this study is to determine incidence of CAUTI amongst patients admitted in the tertiary 364 beds hospital in the United Arab Emirates (UAE), identify the indications for the urinary catheters, understand pathogens causing CAUTI, appropriateness of antibiotics used to treat these cases and mortality related to CAUTI.

METHODS

Settings

This study was conducted from January 2019 until June 2020 amongst patients admitted into a multispecialty quaternary-care Joint Commission international accredited hospital in the UAE - a facility with licensed 364 beds. Of these, 72 beds are intensive care units' beds and 288 acute care beds. The hospital provides specialized care to adults Emiratis and expat population. Patients included were all inpatient who meet the definitions for Catheter Associated Urinary Tract Infections (CAUTIs).

Definitions

We used NHSN definitions as written, where CAUTI is defined as a UTI where an indwelling urinary catheter was in place for more than 2 consecutive days in an inpatient location on the date of event, with day of device placement being Day 1, and an indwelling urinary catheter was in place on the date of event or the day before.
UTI definitions include at least one of the following signs or symptoms: fever (>38.0°C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, and dysuria.
As per our hospital policy, indications for insertion or keeping urinary catheters were (a) undergoing a selected surgery (b) monitoring urine output (c) management of urinary retention or obstruction (d) assistance in sacral pressure healing, and (e) end of life support.

Data Collection

In our facility surveillance data is collected prospectively, is patient based and active. For this study, data was retrospectively collected from three electronic systems.
For the numerator we use EPIC as the electronic medical record (EMR) system; microbiology data is collected form Sunquest laboratory system, and RL infection software is used to perform infection control surveillance. For the denominator data for urinary catheter days is collected electronically through integration between EPIC and RL infection software. Data collected were: patient age, sex, presence of urinary catheter, indications for insertion or keeping urinary catheter, urinary culture, urinalysis, signs and symptoms, antibiotic prescriptions and deaths where CAUTI is mentioned as a cause.
Both numerators and denominators are validated through a vigorous internal process.

Statistical analysis

Descriptive statistics we performed to show rates, percentages, means, standard deviations and medians.
CAUTI rate per 1000 urinary catheter days was calculated using the following formula: *No. of CAUTIs/No of Catheter Days *1000.*
Device Utilization Ratio was calculated using the following formula: *No. of Urinary Catheter Days/ No. of Patient Days.*

RESULTS

Demographic Data

During the study period, 12 patients developed CAUTI. Of these, 11 (92%) were male and only 1 (8%) was female, and the median age was 64 years (Table 1).

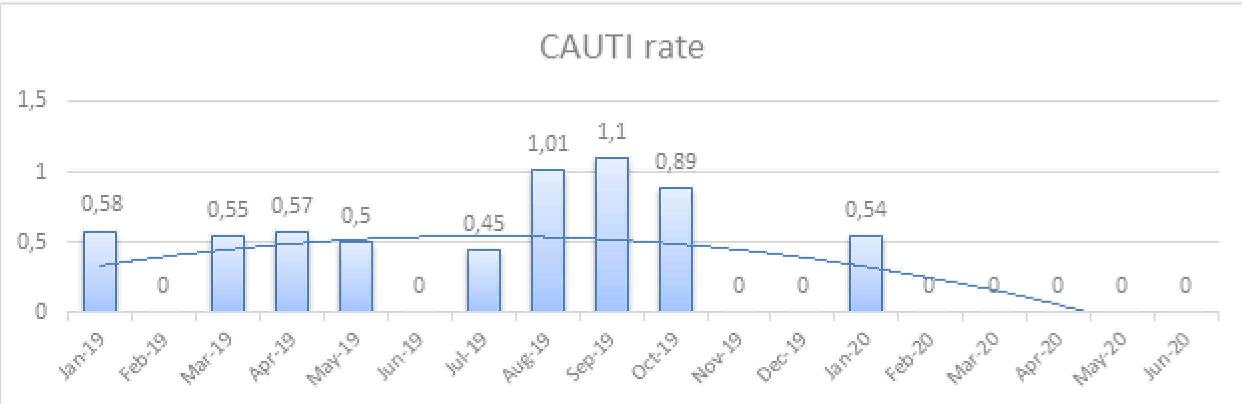
Case #	Age	Gender
1	75	M
2	84	M
3	48	F
4	66	M
5	60	M
6	97	M
7	76	M
8	40	M
9	80	M
10	62	M
11	51	M
12	36	M

Incidence of CAUTI

The overall incidence of CAUTI varied from 0.45 to 1.1 CAUTI/1,000 urinary catheter days. There was a difference of incidence of CAUTI between intensive care units and acute care units where about two-third of cases were reported in the latter. In addition, the overall device utilization ratio ranged from 0.22 to 0.30, with a median of 0.22 (Table 2 and graph 1).

	No of CAUTI	Urinary Catheter days	CAUTI rate	95% CI	Patient days	Device Utilization Ratio
Jan-19	1	1,735	0.6	0-17	6,833	0.1
Feb-19	0	1,666	0.0	_	6,478	0.1
Mar-19	1	1,831	0.6	0-16	6,752	0.1
Apr-19	1	1,752	0.6	0-17	6,581	0.11
May-19	1	2,004	0.5	0-15	6,271	0.14
Jun-19	0	1,935	0.0	_	6,324	0.12
Jul-19	1	2,208	0.5	0-13	6,982	0.12
Aug-19	2	1,978	1.0	0-2.4	6,355	0.12
Sep-19	2	1,818	1.1	0-2.6	6,780	0.1
Oct-19	2	2,241	0.9	0-21	7,146	0.13
Nov-19	0	1,960	0.0	_	6,575	0.13
Dec-19	0	1,775	0.0	_	5,956	0.11
Jan-20	1	1,863	0.5	0-16	6,145	0.11
Feb-20	0	1,823	0.0	_	6,488	0.11
Mar-20	0	1,925	0.0	_	6,735	0.11
Apr-20	0	1,695	0.0	_	6,693	0.11
May-20	0	2,634	0.0	_	7,014	0.17
Jun-20	0	2,084	0.0	_	6,091	0.14
Total	12	34,927	0.3	1.5-5.4	118,199	0.12

Table 2



Graph 1

Indications for insertion and retaining urinary catheters

During the study period, we observed disparities in reasons for insertion and retaining urinary catheters. We reported 52% of urinary catheters were inserted and kept for strict measurement of fluids, 22% for urinary retention, 9% for genitourinary surgery or procedures, 8% for prolonged immobilizations, 5% receiving diuretics and 4% others (Table 3).

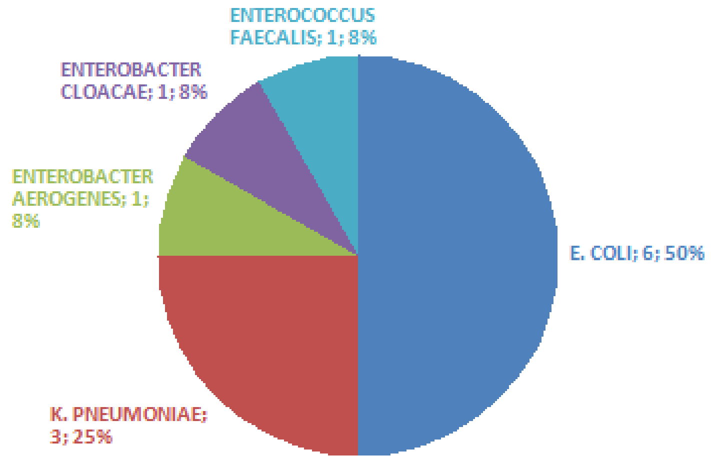
Indications	n	%
strict measurement of fluids	1847	52
urinary retention	780	22
genitourinary surgery or procedures	307	9
prolonged immobilizations	294	8
Receiving diuretics	178	5
Others	136	4
Total	3542	100

Table 3

Uropathogens

The Enterobacteriacae was the most common group of uropathogens (9 episodes, 75%) consisting of *Escherichia coli* (6 episodes, 50%), *Klebsiella pneumonia* (3 episodes, 25%), other gram negative uropathogens (*Enterobacter aerogenes* and *Enterobacter cloacae*, 2 episodes) and gram-positive bacteria (*Enterococcus faecalis*, 1 episode).

UROPATHOGENS



Mortality

Of the 12 patients with CAUTI, there were no CAUTI-related death reported from the study subjects. All patients were successfully treated with the appropriate antibiotics.

DISCUSSION

In our study, we report the incidence rate of CAUTI ranging from 0.45 to 1.1/1,000 urinary catheter days which is below the incidence rate of CAUTI in medical or medical/surgical inpatients reported to the NHSN in 2008 (3.1 to 7.4/1,000 urinary catheter days) (Edward et al, 2009). Conversely, although some studies reported higher incidence of CAUTI in ICU than in non-ICU patients (Lewis et al, 2013), in our study we reported higher incidents of CAUTI in non-ICU(rate/1,000 catheter days) than in ICU patients.

Our study supported the evidence that CAUTI occurs in all hospitalized patients with urinary catheters and therefore prevention strategies should be for both ICU and non-ICU settings (Hidron, et al 2008).

The most common indications for insertion and keeping urinary catheter we found from our study for both ICU and non-ICU patients was strict measurement of fluids (52%), urinary retention (22%), genitourinary surgery/procedure (9%) and prolonged immobilization (8%). We did not perform further analysis to validate appropriateness of these indications but we assumed that some of these urinary catheters were inserted and kept without valid reasons. Our assumptions are supported by evidence from several studies that shows most of urinary catheters are placed for inappropriate reasons and clinicians are often unaware that their patients have catheters, leading to prolonged and unnecessary use and subsequent risk of infections (Munasinghe et al, 2001; Jain et al, 1995). In addition, a national survey study of the US national acute hospitals on urinary catheter use showed that nearly half of urinary catheters were inserted for incontinence and more than a third were inserted for patient/family request (Todd et al, 2014).

Furthermore, the most three frequent uropathogens isolated in our study were *Escherichia coli* (50%) and *Klebsiella pneumoniae* (25%). We did not include CAUTI caused by candida as these are excluded in the NHSN definition for CAUTI. Similarly, *E coli* (21.4%) was the most reported to the CDC's NHSN followed by *Candida spp* (21.0%), *Enterococcus spp* (14.9%), *Pseudomonas aeruginosa* (10%), *Klebsiella pneumonia* (7.7%), and *Enterobacter* (4.1%). In our study we did not include CAUTI caused by *Candida spp* as these are excluded in the current NHSN definition for CAUTI. Curiously, the reason why *Klebsiella pneumonia* was more common than *Enterococcus spp* and *Pseudomonas aeruginosa* remains unclear. However, the reason for high incidents of CAUTI caused by *Enterobacteriaceae* (e.g. *E coli, Klebsiella pneu-*

monia) is that usually bacteria from this family enter the bladder through extraluminal migration from rectum colonizing the patient's perineum given the physiological proximity between the urethral and rectum (Tambyah PA et al, 1999).

Moreover, we did not find CAUTI to be associated with mortality in both ICU and non-ICU patients in our study. We did not measure the effect of CAUTI in length of stay. In the same vein, a systematic review conducted to measure relationship between CAUTI and mortality in ICU patients show no relationship (Chant et al, 2011). Although an overall morbidity and mortality from CAUTI is considered to be relatively low compared to other HAIs, the burden of urinary catheter use leads to a large cumulative incidence of infections with resulting infectious complications and deaths (NHSN, 2019).

Shafi Mohammed, DNP, MPH, BSN
Shafi serves as a director of infection control and a co-chair of Cleveland Clinic Abu Dhabi Infection Control Committee. He holds a doctorate from Case Western Reserve University, Ohio (USA) and a Master degree in Public Health from Oxford Brookes (UK). Previously, he served as Head of Infection Control Services in primary health care facilities for the National Health Services in the UK, and a managing director of Fleming Healthcare Ltd (UK) He is a fellow of the Royal Society of Public Health (UK), a member of Association of Professionals in Infection Control and Epidemiologists (APIC) and a member of the Board of Directors for APIC UAE Chapter.

Elias Tannous, MBA, BSN, CIC
Infection Control professional with extensive IC experience. He has been heavily involved in major infection control activities, projects and programs, this includes commissioning of new facilities, developing surveillance programs and evaluating IC programs. In addition, he coordinated and facilitated loads of IC educational activities. He is the founder of the Arab Countries Infection control Network (ACICN), serves as a board member on several Infection Control entities, and in 2020, he was appointed as an international ambassador for infection control, a program by the Society of Health Care Epidemiologist of America (SHEA). He currently serves as a Senior Infection Control Practitioner at in Cleveland Clinic Abu Dhabi.

Ahmad Nusair, MD, FACP, FID SA, FSHEA
Dr. Nusair graduated from Jordan University of Science and Technology and completed his residency training in Internal Medicine at Western Reserve Care System, Ohio. He also completed his Fellowship in Infectious Diseases at Creighton University and University of Nebraska Medical Center in 2007 and his fellowship training in Critical Care Medicine at Mayo Clinic, Minnesota. Currently Dr. Nusair chairs the Infection Control Committee at Cleveland Clinic Abu Dhabi and is currently the Program Director for the Internal Medicine Residency.

Claire Nolan, MSN-IC, BSN 1
Claire Nolan completed her nursing degree in University College Dublin and her Masters in Nursing specializing in Infection Prevention and Control in Royal College of Surgeons Ireland. She has worked in Ireland and Australia before emigrating to Abu Dhabi where she works as a Senior Infection Control Practitioner in Cleveland Clinic Abu Dhabi.

References

(1) Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: Antimicrobial-resistant pathogens associated with health-care-associated infections: Annual summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2006-2007. Infect Control Hosp Epidemiol. 2008;29(11):996-1011.

(2) Magill SS., O'Leary SJ. Janelle DL., et al. "Changes in Prevalence of Health Care Associated Infection in the U.S. Hospitals". New England Journal of Medicine" 379: (2018) 1732-1744.

(3) McGuckin M. The patient survival guide: 8 simple solutions to prevent hospital and healthcare-associated infections. New York, NY: Demos Medical Publishing; 2012.

(4) Lo E, Nicolle LE, Coffin SE, Gould C, Maragakis LL, Meddings J, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. Infection Control and Hospital Epidemiology 2014; 35:464-79.

(5) https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf.

(6) Scott Rd. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention, 2009. Division of Healthcare Quality Promotion, National Center for Preparedness, Detection, and Control of Infectious Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, February 2009.

(7) Klevens, RM., Edward, JR., et al. "Estimating Healthcare-associated Infections and Deaths in U.S. Hospitals". Public Health Reports 122: (2007):160-166.

(8) Munasinghe RL, Yazdani H, Siddique M, Hafeez W. Appropriateness of use of indwelling urinary catheters in patients admitted to the medical service. Infect Control Hosp Epidemiol. 2001;22(10):647-649.

(9) Jain P, Parada JP, David A, Smith LG. Overuse of the indwelling urinary tract catheter in hospitalized medical patients. Arch Intern Med. 1995;155(13):1425-1429.

(10) Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. Am J Infect Control. 2000;28(1):68-75.

(11) https://www.cdc.gov/infectioncontrol/pdf/guidelines/cauti-guidelines-H.pdf

(12) Tambyah PA, Halvorson KT, Maki DG. A pro¬spective study of pathogenesis of catheter-associated urinary tract infections. Mayo Clin Proc 1999; 74: 131-6.

(13) Todd Greene, Kiyoshi-Teo, HK., Reichert, H., Krein, S., & Saint, S (2014). Urinary Catheter Indications in the United States: Results from a National Survey of Acute Care Hospitals. Infect Control Hosp Epidemiol 2014;35(S3):S96-S98.

(14) Chant, C., Smith, O.M., Marshal, J., Friedrich, J.O. (): Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: A systematic review and meta-analysis of observational studies. Crit Care Med 2011 Vol. 39, No. 5.

FIELD EXPERIMENTS AGAINST RISKS FOR WOMEN GIVING BIRTH IN SUB-SAHARAN AFRICA

"Field experiments to reduce coronavirus / AMR infection risks for women giving birth in Sub-Saharan Africa, and to reduce gender bias in health care".

Abstract

The *JamboMama!* programme seeks to reduce maternal mortality and morbidity by improving the communication between health seeker and health provider, increasing knowledge about pregnancy and recognising danger signs, and reducing the three deadly decision-making delays that can cost or maim lives of mothers and babies. We refer to the delay in seeking qualified, modern trained help, the delay in accessing the right place of care, and the delay in getting the care needed once arrived. Further research and multidisciplinary discussion are required to adjust this project's assumptions. Not only at the international level, but right where it hurts and where it matters: where women give birth in under serviced areas.

> ***"The SAHFA (Smart Access to Health for All) program using the JamboMama! communication tools seeks to combat the risks of infections acuired in health care, including AMR and COVID-19 infectious diseases, as well as to improve women's rights and safety during pregnancy and in maternity care, at all levels."***

Laetitia van Haren, Cultural Anthropologist, Rijksuniversiteit Utrecht,The Netherlands

This policy paper makes some suggestions based on the limited field experience we have by now developed with our *JamboMama!* programme. This programme seeks to reduce maternal mortality and morbidity by improving the communication between health seeker and health provider, increasing knowledge about pregnancy and recognising danger signs, and reducing the three deadly decision-making delays that can cost or maim lives of mothers and babies. We refer to the delay in seeking qualified, modern trained help, the delay in accessing the right place of care, and the delay in getting the care needed once arrived. Further research and multidisciplinary discussion are required to adjust this project's assumptions. Not only at the international level, but right where it hurts and where it matters: where women give birth in underserviced areas. In homesteads, clinics and rural hospitals, discussions between women and men, in communities, between first line health workers, horizontal and vertical from the homestead to the district hospital where emergency obstetrical care is available and back. That entry level horizontal and vertical discussion and collaboration is not facilitated at this point. The facilitation ought to start at best at the regional level towards the ministerial level and back, with horizontal discussions at both ends.

The regional level is expected to know what the district level needs. The district level is expected to know what the homestead level needs. But is there a dialogue? Would the dialogue and discussion towards safer, more effective, more respectful and efficient maternal and newborn care become more fruitful with a customised IT tool supporting facilitation? This is what SAHFA (Smart Access to Health for All) tries to explore by creating tools that can fill that gap. These tools will also help with the discussion about COVID-19 prevention and containment and in general help to analyze and find local, affordable solutions to prevention and containment of all infections, from banal ones to complicated ones. From those that still respond perfectly well to cleaning and "light" disinfection (bleach, vinegar, bicarbonate of soda, alcohol and iodine based), to disinfection that requires more aggressive means; the infections (parasitical, viral, microbial, fungal) that require special pharmaceutical products but which still have a pharmaceutical enemy that can overcome them. And finally, the infections that have become antimicrobial resistant (AMR), or do not yet have any treatment as the coronavirus SARS-CoV2. Let us first help the entry level health care sector directed by district level authorities to get a grip on those infections that are still preventable at low cost, with simple means, and a basic level of health literacy.

Underserviced. This implies the quality is low and the quantity is insufficient - of virtually everything - except for the number of women needing better quality of care, including protection from infection risk - not only from germs and viruses that have become AMR, or do not have treatment, as COVID-19, but even from those that can be controlled with classical hygiene, disinfection and sterilisation. Underserviced means inadequate quality and quantity of trained staff, of materials and medication, of knowledge and communication. The lack of hygiene is among the shortages.

Means are insufficient where even clean drinking water is a rarity, yes water itself is in short supply. The same goes for soap, for clean towels, and so further. Sterilisation of operating theatre material and protective clothing of the surgical staff is nevertheless often well taken care of even in rural hospitals in low resource settings. I found that often there is one person solely responsible for the whole process (sometimes assisted, but often single handed) and this person takes great pride in doing the job right, even if the means are inadequate by modern standards.

> **But overcrowding, with different women, too quickly one after another, or even sometimes simultaneously, using the same bed during labour and the same delivery room and the same delivery bed used for one woman after another without proper cleaning, let alone disinfection in between the patients, leads to perinatal and nosocomial infections that could be prevented. In rural health facilities of any size, infection risk from microbes and viruses that are not multi-drug resistant is still high.**
>
> **In the framework of the *JamboMama!* project we have written a few fact sheets for rural health workers to make antenatal consultations safer and to share information with women on how they can keep themselves and their unborn babies safe from COVID-19.**

For our project's objective the COVID-19 acted more as a wake-up call about the importance of proper hygiene for pregnant, parturient and postpartum women in general. It reminds us that we must make sure our *JamboMama!* app raises awareness

in a concrete and practical manner as to how to improve personal, family, community and antenatal clinic hygiene to avoid preventable infection[1].

Are we reducing gender bias at the same time? Yes! We do so by emphasising it, for we seek to empower women, giving priority to them learning about pregnancy and how to use a smartphone. We encourage them getting help from their children or younger sisters and brothers. There is no other way to overcome the gender bias that gives pregnant women a low status than to give them extra help to overcome the health challenges linked to their female reproductive function at the root the gender bias. How? By compensating with extra care and self-improvement for the risks directly linked to their female sex based vulnerabilities.

We at SAHFA recognise that is due to women's low status that excess maternal mortality perseveres, of which 10% is due to infections incurred during pregnancy, at childbirth or during postpartum. But this 10% figure is for sub-Saharan Africa as a whole. Zooming in on hospitals and dispensaries in underserviced and overpopulated areas we will find much higher rates of infection. A nurse told me that in the paediatric ward of the hospital where he works, infections affecting mothers and babies and picked up during delivery or right after are frequent, with sometimes serious consequences, from disabilities to death for either or both. These infections are due to poor hygiene, to low allocation of means and efforts to hygiene, again acerbated by the general indifference with which the huge mortality and morbidity risks of mother and child are viewed in too many places in the world. This is changing, but not fast enough and not widely enough. Precisely because women and children have such a low status, because they depend on the benevolence of others, life threatening negligence can persist.

The protection of your life, your health and your well-being is a matter of entitlement. Benevolence helps claim, not replace entitlement. In global statistics for maternal death in sub-Saharan Africa, infections count for only 3% of all maternal deaths, though WHO puts the figure at 10%. The disparities in SSA are such that either figure lumps together figures close to EU standards and those well below the national average. The biggest threat for the mother remains HIV (and other STDs) at present. In other words, a virus that is very difficult to control because it is resistant to many low-cost broad spectrum antiviral drugs.

To this omnipresent risk we have to add COVID-19 now. Not much is known in remote areas of Tanzania such as the area where we introduced our *JamboMama!* for Safe Motherhood programme, only that is doesn't seem to be spreading much in remote and underserviced districts yet.

So we continue to view the COVID-19 threat in the area we target as a wake-up call to infection prevention. What action do we propose then, based on our limited field experience with the *JamboMama!* concept and app, born out of much wider and vaster indirect knowledge? The author's input in the ground level debate and reflection is based on 50 years of "free" desktop and anthropological field experience. "Free" refers to socio-cultural and medical anthropology experience unrelated to the *JamboMama!* pilot, now fed into the objective of reducing maternal and infant mortality and morbidity from all causes, including preventable infections.

SAHFA's proposed policy is to strengthen local collaborative action based on shared understanding of the issues at stake, shared agreement on the need to tackle them and an emotional and normative framework that includes those most marginalized and recognises pregnant women and their to-be-born, newly born and older infants as human beings with full rights to protection to the measure they need it. So if they need more care than your average healthy young or older male, they have a right to that more and better. And all stakeholders must agree that this is not unfair. It ensues that low level health and social welfare decision makers, including or even most importantly the men among them and men in general, have to be willing contributors, participants and facilitators of the process, and be willing to let it travel up via the regional to the ministerial level. We as global health activists should give them a hand through knowledge sharing and advocacy with projects that help them carry out what they collectively propose and agree to. We try to tackle the communication gap between health seekers and health providers. More effective communication around the dangers of pregnancy and how to make a pregnancy safer and happier for mother and child (and therefore for the whole family and the community) must include lessons in hygiene.

COVID-19 has made us aware of that. Personal, family, community and rural health facility hygiene. We should discuss the steps that can be taken. Starting with the simple, affordable steps that demand more of a discipline and behaviour change than money. We cannot escape behaviour change, no amount of money can do it for us in ways that allow us to remain in the slumber and sloth we are used to and feel comfortable with. This "we" includes all of us as human beings. *JamboMama!* is also a wake-up call at the local level. The measures to combat infection around pregnancy and childbirth include better hygiene, (the simple measures discussed on page 1), such as social (and practical) distancing and handwashing. They include better toilet and respiratory hygiene and discuss ways to achieve it at home, and in the dispensary and hospital.

The distancing is served by better spread of the parturient mothers over various health facilities by better referral. Better referral is possible if the *JamboMama!* app is used in the maternal care system connecting the different levels of obstetrical care available and their distance towards the patient (through the near-me function). It also involves setting up separate centres, on the premises of bigger hospitals to avoid contamination and by building birthing centres closer to the villages where women live. Those centres should have a qualified midwife available and on call 24/7. well trained in labour management, who is given the means to implement the rules of hygiene required in obstetrical care. One step closer to the actual homesteads and one step further in avoiding peri, intral and postanatal nosocomial and opportunistic infections is to have a team of midwives with one or two obstetrical surgeons among them who can go by motorcycle ambulance to certain spots created for that purpose where they can fold out a treatment tent that the motorcycle ambulance provides.

This does not take care of the infections that the mothers themselves may have and that reveal themselves at birth, such as HIV, tetanus, malaria, TBC. But most of these infections will have been detected well before, as the mother is registered with the *JamboMama!* app. The medical background of that app and the regular "Vital Info Updates" it asks from the registered mom (to be done with a qualified health provider to do the check-ups and help fill out the answers correctly) requests the mom to have herself tested for these infections and to report other issues she may have (e.g., disabilities, cardio-vascular disease, etc.). The roving midwives can therefore bring and prepare for the cases they will meet that day including the 15% unpredictable life threatening surprises. But for those irrepressible obstetrical emergencies the *JamboMama!* birthing centres are connected with the level 3 hospital that has an operating theatre where c-sections can be done and all the supplies for obstetrical emergencies are present, including for correct disinfection, sterilisation and combating multi-drug resistant germs, viruses and fungi. The *JamboMama!* app helps build the capacity of community members to learn about good practices and expectations upon visiting a healthcare provider, so there is natural pressure on the health care facilities to perform better, including in matters of hygiene. For nothing abhors pregnant women who must give birth more than to have to lie in a dirty environment with the touch, feel and smell other women's private bodily excretions. Asked why they loved a certain dispensary so much for giving birth, they answered that they got a clean delivery bed, could go and have a nice warm shower after the birth and could lie resting in a clean bed with their new baby until someone came to pick them up and bring them home.

The hygienic conditions were the first they mentioned. Of course, the extreme gentleness and courtesy of the staff also weighed heavily, but it was striking that the possibility to shower afterwards and to give birth in a clean environment came first, before the meal and all the rest.

My second point is an emotional one. The mother's human right to dignity and hygiene should put a halt to the building of massive delivery rooms where several women have to deliver in full view and hearing of each other. Women loathe this. Young girls are terrified, mature women feel vilified. Even supportive fathers cannot attend the birth of their child.

If farmers make sure a cow that needs to calve has a quiet, dimly lit clean and PRIVATE corner to do this, why don't women, human mothers, have the right to privacy and kindness? Why must they be sacrificed to efficiency with increased risk for the spread of infections?

Therefore, in current times of an infectious crisis such as COVID-19, but also for other epidemics that may occur, a district could have trained midwives (men and women) who drive a motor ambulance that can be unfolded like a tent where a woman could give birth safely and in dignity, supervised by a trained midwife equipped with what is needed for a vaginal delivery with eventually use of vacuum extractor and episiotomy.

Caesareans would have to be taken care of in a proper theatre, but those birthing centres would be in contact with the nearest level 3 hospital where maternity-related emergencies can be brought to. This can be done through the *JamboMama!* app or any other smartphone and cellphone based alarm system that connects a web of level 1 and 2 dispensaries with a health centre and hospital where caesareans can be done, where there is blood plasma available and oxygen. The better spread of the obstetrical burden would mean lower infection risk. But the fact that service use is better spread means there is time between patients to disinfect and sterilise correctly.

These entry-level efforts need guidance and support from the higher levels connected to the top, and directly from international expertise given in solidarity, not for profit. Only then can the locally responsible key persons, from the mothers and their communities to the first line antenatal clinic attendants to the midwives and medical authorities truly grasp what giving birth in dignity means. For mother and child to survive in the best health nature gave them is a right that we must collectively ensure and whose fulfilment should neither be seen as a moneymaker, nor as an act of charity. Women's survival has no price. It must be achieved together by joint efforts, including in the combating of infections whether banal, specific, nosocomial, ante, intra or postnatal. Let us start where it hurts! The actors are ready!

Laetitia van Haren, Cultural Anthropologist, Rijksuniversiteit Utrecht,The Netherlands. Founder NGO SAFHA.
1972-75: North Kivu, Congo, as teacher of English.
1976-1978: Lesotho, where she completed her academic fieldwork on the impact of migration on village life and consultancies for rural community development projects.
1979-1980, Somalia: research in refugee camps and volunteering at a hospital in Mogadishu, where she discovered the ravages of infibulation and of very young girls given to much older men in marriage.
1986 -2011 Then Senegal, Congo again, Laos, Haiti, in between bouts in Geneva of policy planning and implementation on refugee assistance in NGOs and as UNHCR consultant, access to health for all advocacy, a CEO position with a children's rights NGO and a faith based humanitarian aid NGO, working with and travelling to Africa.
2011-2019, Field officer for DCC, a volunteer training and sending NGO in France to coach volunteers going to and working in South-East Asia (once a year field visits and distance coaching).
Since 2015, focus on a) reducing rural maternal mortality and improving pregnancy and child birth outcomes through the interactive smartphone application *JamboMama!* b) bring digital literacy for smart access to health to undersourced areas, to bridge the communication gap between health seeker and health service provider.
2011-2019, Field officer for DCC, a volunteer training and sending NGO in France to coach volunteers going to and working in South-East Asia (once a year field visits and distance coaching).
Since 2015, focus on a) reducing rural maternal mortality and improving pregnancy and child birth outcomes through the interactive smartphone application *JamboMama!* b) bring digital literacy for smart access to health to undersourced areas, to bridge the communication gap between health seeker and health service provider

References

Hanson C, Cox J, Mbaruku G et al. Maternal mortality and distance to facility-based obstetric care in rural southern Tanzania: a secondary analysis of cross-sectional census data in 226 000 households. Lancet Glob Health. 2015; (published online May 22.) http://dx.doi.org/10.1016/S2214-109X(15)00048-0 In The Lancet Global Health, Claudia Hanson and colleagues present their study of access to obstetric care in Tanzania. Their approach illustrates how risks of maternal mortality can be clarified in the difficult conditions of rural Africa. Hanson and colleagues also found high pregnancy-related mortality of 664 deaths per 100 000 livebirths even though 72% of women gave birth in hospital and 8% had delivery by caesarean section.

Preventing Maternal Deaths in Africa | | Blogs | CDC
blogs.cdc.gov/global/2014/03/03/preventing... 03/03/2014 · Here' the kicker: while estimated maternal mortality ratios have been cut almost in half over the past 20 years worldwide, maternal mortality actually appears to have increased in eight countries in sub-Saharan Africa with high HIV prevalence.

Disease and Mortality in Sub-Saharan Africa. 2nd edition.Chapter 16, Maternal Mortality Khama O. Rogo, John Oucho, and Philip Mwalal. Laetitia van Haren: Dangers for pregnant, parturient and postpartum mothers related to the coronavirus epidemic. Online on SAFHA Website, April 2020; Same author: Health Literacy For Vulnerable Communities at the Time of Corona. May 2020 ; Same author : Pregnancy and Breastfeeding During The COVID-19 Pandemic: A fact sheet for maternal and newborn care providers in rural areas of Subsaharan Africa and for mothers literate enough to read this text. May 2020; Same author: Protecting Pregnant Women From CORONA Virus Disease 2019 (COVID-19) in Rural Communities of Subsaharan Africa KUWAKINGA WAJAWAZITO DHIDI YA VIRUSI VYA CORONA. April 2020

1) Laetitia van Haren: Dangers for pregnant, parturient and postpartum mothers related to the coronavirus epidemic. Online on SAFHA Website, April 2020; Same author: Health Literacy For Vulnerable Communities at the Time of Corona. May 2020 ; Same author : Pregnancy and Breastfeeding During The COVID-19 Pandemic: A fact sheet for maternal and newborn care providers in rural areas of Subsaharan Africa and for mothers literate enough to read this text. May 2020; Same author: Protecting Pregnant Women From CORONA Virus Disease 2019 (COVID-19) in Rural Communities of Subsaharan Africa KUWAKINGA WAJAWAZITO DHIDI YA VIRUSI VYA CORONA. April 2020

2) Alvarez, J.L., Gil, R., Hernández, V. et al. Factors associated with maternal mortality in Sub-Saharan Africa: an ecological study. BMC Public Health 9, 462 (2009). https://doi.org/10.1186/1471-2458-9-462 « Maternal deaths result from a wide range of indirect and direct causes. The major direct causes in Africa are haemorrhage (34%), infection (10%), hypertensive disorders (9%) and obstructed labour (4%). »

ONE HEALTH
AMR THINK-DO-TANK
GENEVA INTERNATIONAL

SECTION VII

ONE HEALTH IS NOT EQUIVALENT TO GLOBAL HEALTH

Abstract

The concepts of Global Health, One Health, and Solidarity are often used separately when discussing emerging diseases and how we can control them. The current COVID-19 pandemic profoundly influenced these discussions. Here, we explore why articulating these three concepts might significantly increase our effectiveness against current and future pandemics.

"

COVID-19 as a Game-Changer
Putting Solidarity at the Cross-Road of the Global Health and One Health Concepts
a necessary positioning against current and future emerging diseases

"

Antoine Andremont, MD, PhD., Emeritus professor, University of Paris, France,
Participant, Global AMR R&D Hub, Germany

COVID-19 is a game-changer and an incentive to change the way we think health matters.
The COVID-19 epidemic which disrupts life and economies worldwide is a game-changer in the manner we encompass health. Before it occurred most experts and most decision-makers had the idea, which indeed was rather well supported by facts, that although health was a topic of major importance which needed continuous efforts and increased spending, the threats that it imposed to humankind were somewhat addressed by the systems and organizations that we had put in place.

Even if only in part, things were more or less contained. Global malnutrition was receding, historical epidemics were behind us, and even for HIV/AIDS some hope was emerging. According to UNAIDS, around two-thirds of the 38 millions human beings living with HIV had access to treatment in 2019. The last recent threats of emerging viral diseases, including Ebola, SARS, MERS, had been controlled with or without available vaccines or highly effective drugs.

Only antimicrobial resistance (AMR) was still fully out of control and appeared little susceptible to the classical control measures that we had developed. The idea among experts was that it was because its genesis was of a somewhat different nature than that of classical infectious diseases. It appeared to be very much linked to the global impact of human civilization and behaviors which culminated in the so-called globalization process.

Global Health, One Health, and Solidarity, each on their own path. Three concepts developed fairly independently over the last decade among circles that have dealt with the topic of Health in a global manner.

GLOBAL HEALTH

The first one is the concept of Global Health.
Global Health hypothesized that no country, no group of humans, is isolated when health is concerned. What happens in any place on earth in a certain group of people may, and often will, influence what happens in other groups. In the pre-modern era, when people were not moving much from their usual place of living, many diseases had much less chance to move around and spread. The risk of dissemination of pathogenic microbes has increased over time in parallel with travel and interconnections at the surface of the globe. In a way, Global Health is an extension to a specific field or niche of the Global Village concept, which the Canadian theorist Marshall McLuhan popularized in the sixties. He was then speaking of the media and describing the world as tied together into a single globalized marketplace and village.
Indeed, even if infectious diseases are at the forefront of today's concerns, the Global Health concept is not restricted to infectious diseases. For instance, the massive epidemic of obesity and of its related metabolic consequences that we observe in most parts of the world is closely linked to the dissemination of dietary and cultural habits that have originated in the Western world and particularly in North America. Certainly, the media of the "global village" have been here of major importance to drive this real pandemic.
Global Health takes all that into account and tries to elaborate on strategies and politics that aim to deliver global solutions that can be applied everywhere, even if local adaptations have often to be added.
There is another facet of globalism that should not be forgotten when health is considered: an intervention focused on a specific disease can have consequences on others. For instance, mass azithromycin administration, recommended by the World Health Organization (WHO) to eradicate both trachoma and yaws, could have the general effect of reducing overall mortality by 13.5% in under-5 childhood. This also reduces certain gut bacteria, including known pathogens. However, at the same time, it can be selecting for antibiotic resistance with serious long-term consequences[1].
Another example of globalism is observed right now during the COVID epidemic. The WHO has newly emphasized the need to integrate the culture of Infection Prevention and Control (IPC) into the basic function of health systems globally in order to control outbreaks of COVID-19 today[2]. As a result, IPC has probably never been more emphasized in health centers and implementation would result in a welcomed decrease of AMR infections.

ONE HEALTH

The second concept is that of One Health which is indeed very different. One Health is not a geographical concept. It is a transectorial one: the health of humans is not independent of that of animals and even of that of the environment.
One Health in practice results from the collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals, and our environment. Even if, in the end, the health of humans is the most important to preserve, the One Health concept recognizes that this cannot be achieved without taking care of the health of the living components of the two other sectors, i.e. the animals and the environment.
Indeed, the recognition that environmental factors can impact human health can be traced as far back as Hippocrates. Nevertheless, it was only early in the 20th century that it was well established that a number of human diseases originate in animals. Then, the concept of zoonosis emerged.

However, the One Health concept per se is junior with regards to the Global Health one. It really gained momentum only at the turn of the millennium. It was then linked, notably, to the emergence of the antibiotic crisis linked itself to antibiotic overuse in humans, animals, and agriculture generating the fear that untreatable bacterial infections would jeopardize the progress of medicine in humans[3].
The One Health Initiative Task Force was established in 2006 by the American Veterinary Medical Association; the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was created in 2008 and lasted 10 years. In April 2010, a Tripartite concept note announced collaboration between the WHO, the OIE, the FAO for sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interfaces. This tripartite organization, a secretariat of which has been established in 2012, has been very important in the definition of the means to fight antimicrobial resistance. Today the UN Environment Program, UNEP, is also "on board" of what is called the "Tripartite Plus" organization and a formal relationship between the four organizations is being explored.

Recently, with the development of the COVID-19 epidemic, One Health has appeared as a key concept to explain the emergence of new diseases due to animal microbes. It is now clear that the concept has to be put forward in any attempts to elaborate prospective measures to protect the future from such catastrophes.

SOLIDARITY

The third concept that is important for us today is that of Solidarity. It is very different in nature. Often, it is presented as an obligation for high-income countries to alleviate the burden that many diseases impose on low and middle-income ones. The term is not coming from the Health domain but from that of human and social sciences, having been put forwards, for instance, in the late 19th century by Emile Durkheim in his theory of the development of societies[4].

Concerning Health, Solidarity has emerged at about the same time as Henri Dunant created the Red-Cross to help wounded soldiers of any faction or country at war[5].
However, more recently, it is certainly the action of the so-called "French Doctors" during the Biafra Independence[6] and the subsequent creation of the "Doctors without Borders" organization under the leadership of Bernard Kouchner, soon followed by others, which put the concept of international solidarity for Health at the forefront of progress. During the last decades, we have observed a myriad of initiatives both from the public and the private sectors, aiming at the relief of the pains and suffering from infectious diseases, which were based on the solidarity of the high-income countries towards low or middle-income ones. Public initiatives such as UNITAID and the Global Fund to Fight AIDS, Tuberculosis and Malaria, charities such as the Bill and Melinda Gates or the Mérieux foundations can be cited, among many others.
During the current COVID-19 pandemic, solidarity has been shown, for instance, with the launch April 2020 of the Access to COVID-19 Tools Accelerator (ATC-A) initiative. ACT-A defines itself as a ground-breaking global collaboration to accelerate development, production, and equitable access to COVID-19 tests, treatments, and vaccines[7].

In April 2020 also, at a virtual summit of the Group of 20, world leaders agreed to pause debt payments of the poor countries. But it may turn out that these efforts are not fully effective and it has been suggested that the World Bank and the International Monetary Fund might have failed to translate their concern into meaningful support[8,9].

STRUCTURING THE CONCEPTS TOGETHER TO INCREASE THEIR EFFICACY

It may be obvious that each of the three concepts described above is extremely powerful to drive hypothesis on the origin and solutions for the control of emerging diseases.
Currently however they are used mostly independently one from another. The difficulties that we experience to control the current COVID-19 pandemic might suggest that a better approach could/should be implemented.

We would like to point out here that these difficulties, or at least part of them, could be due to a lack of structuring of the efforts deployed in the use of the One Health, Global Health and Solidarity concepts. This proposed approach would be based on a better articulation of these three concepts, which might not currently be enough interconnected. It can be observed that people using each of them have a tendency to work in silos. Also, there can be, sometimes, some confusion as to the borders that limit each of the concepts, particularly with regards to the differences between One Health and Global Health. Many people do not have a clear idea of what really differentiates them when, in fact, Global Health and One Health are not on parallel tracks when emerging diseases are concerned.

Take for instance AMR: genes or bacteria, that are the bulk of the problem, navigate easily between the human, the animal, and the environmental sectors, sometimes back and forth. Evidently, a typical One Health problem. However, these bacteria and genes can also navigate geographically all over the world with humans that are often asymptomatic carriers of these bacteria and genes in their intestinal microbiota. The same is true for food producing animals and products. Thus, also a typical Global Health problem. Now, a key factor is that the crossroad of these various flows often occurs in low and middle-income countries where antibiotic usage is poorly regulated, while the food industry export local products to high-income ones. The low and middle-income countries have no way to stop these processes by themselves. So to control the problem of AMR it is also at this crossroad that we have to apply Solidarity, the third of the three concepts described above.

The same reasoning could be applied to the emergence of viral diseases even if the place where Global Health and One Health concepts cross each other may change with each disease. For instance, for diseases that originate from wild animals, Solidarity has probably to be applied to the control of the very beginning of the process of viral transmission from the wild animals to humans or domesticated species. The reasoning can also be applied for non-infectious pandemics such as obesity that we discussed previously. In that case, the cross between one health (fat animals and fat humans are usually living closely…) and Global Health (the obesity pandemic originated in High-income countries before spreading with occidental culture and food habits) and thus, in that case, solidarity to

protect the whole planet should be applied in those countries where the problem originated.

BY NO MEANS A GLOBAL SOLUTION, JUST A PRACTICAL TOOL FOR ACTION

These short lines of thinking must not be taken as a global solution to solve each and every question concerning One Health, Global Health or Solidarity. That would be highly presumptuous and, even more importantly, obviously false.

Indeed, assistance programs have also to focus on other key points, such as, among others, the development of health systems, education, training, and social services.

However, it has, we believe, two merits. First, it will help to destroy silos in which too often specialists are enclosed. Second, it will focus the attention of decision-makers on the specificity that exists for each and every health question and, thus, it might help them in their tasks.

I would say the method has to be taken just as, when cooking, one uses basic principles to mix oily and watery components, or sweet and salted ones to end up with digest, nutritive and tasty food!
In that sense "Putting Solidarity at the cross-road of the Global and One Health concepts" might contribute significantly to increase the efficiency and efficacy of the budgets that we can devote to the sustainable prevention and control of emerging diseases.

Antoine Andremont, MD, PhD, is currently scientific adviser at the Minister of Health of France, notably participating in the Global AMR R&D Hub (a German initiative, now with the G20 countries). Primarily trained as a paediatrician he is retired from the University of Paris Medical School where he was Professor of Microbiology and Head of the Bacteriology Laboratory from Bichat University Hospital in Paris.
He was a member of the 2010-2018 WHO-AGISAR expert advisory group, which initiated the One Health approach in the field of antimicrobial resistance.
Scientifically, he has largely contributed to the understanding of how bacterial resistance emerges in the intestinal microbiota during antibiotic treatments, and, from there, disseminate and/or cause infections with over 280 co-authored scientific publications and books on AMR for a general audience. He has been the scientific founder of the Biotech DaVolterra which develops means to counteract antibiotic resistance.

References

(1) Thuy Doan et al., Gut microbiome alteration in MORDOR I: a community-randomized trial of mass azithromycin distribution. Nat Med. 2019, Sep;25(9):1370-1376

(2) https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC-2020.4

(3) Critical Knowledge Gaps and research needs related to the environmental dimensions of antibiotic resistance. Joakim Larsson et al. Centre for Antibiotic Resistance Research, University of Gothenburg, Sweden. https.//doi.org/10.1016/j.envint.2018.04.041 (Jan 17, 2018)

(4) http://www.actforlibraries.org/emile-durkheim-and-social-solidarity/

(5) https://www.icrc.org/en/doc/resources/documents/misc/57jnvq.htm

(6) https://www.msf.org/who-we-are

(7) https://www.who.int/initiatives/act-accelerator

(8) https://www.nytimes.com/2020/11/01/business/coronavirus-imf-world-bank.html

(9) World Health Organization Executive Board meeting Oct 5 & 6 2020 (online). Member States speaking for the AFRO region, and even the WHO Regional Director for Africa, Dr. Matshidiso Moeti, highlighted the need for debt moratoria, a very unusual 'economic' demand in such meeting.

THINKING ANTIBIOTIC RESISTANCE OR THE PROSPECT OF AN INTERNATIONAL "ONE HEALTH" PUBLIC POLICY

Inspired by an exchange with Jacques Fouad Acar

Abstract

Our logistic approach to the phenomenon of antibioresistance ‘antibiotic stewardship’, though effective, shows limitations as not only is it insufficient, it also distracts us from unresolved issues. The standardisation of international health policies - dangerously flirting with sanitary colonialism, the blaming of the different parties, the inadequacies of the health practitioner's traditional role, are so many factors that hinder our capacity to implement the nonetheless universally welcomed One Health approach. The emblematic case of antibioresistance must incite questioning not solely on technical, but on ethical matters, as encouraged microbiologist Jacques Fouad Acar. An homage to these reflections.

> “ ***Jacques Fouad Acar, a famed French microbiologist, specialised in infectious diseases and in the antibioresistance phenomenon, insisted on the need to rethink this ideological tendency of uniformisation, legitimised by supposedly scientific and rationalist arguments, that in fact shelters a form of sanitary colonialism from which we absolutely must extract ourselves.*** ”

Léonie Varobieff, Consultant, lecturer and expert in philosophy, PhD candidate in Philosophy, Université Jean Moulin, Lyon, France

Adapting to the antibioresistance phenomenon, through prevention measures as well as through deep changes in our practice of healthcare, constitutes an orientation in international public health policies that seems to be unanimous.
At the same time, the ‘One Health’ project had been endorsed as an international common goal by the World Health Organization (WHO), health institutions and actors of the health sector.

To this day, however, many questions remain unsolved that hinder the implementation of such measures; antibioresistance thus becoming an ideal opportunity to evaluate our ability to concretely approach health in its global essence, heeding the interdependency of the Living.

Among the many questions to be addressed, the one pertaining to the imposed standardisation of healthcare practices and policies appears crucial. Jacque Fouad Acar, a famous French microbiologist, specialised in infectious diseases and in the antibioresistance phenomenon, insisted on the need to rethink this ideological tendency of uniformisation, legitimised by supposedly scientific and rationalist arguments, that in fact shelters a form of sanitary colonialism from which we absolutely must extract ourselves.

Furthermore, if we intend to act effectively in the face of antibioresistance, which weakens our public health system, our starting point must be one that considers the existing state of things, rather than an aggressive attitude towards bacteria -which is most commonly adopted amongst health actors.

In many regards, the “struggle” led by medical scientists against infectious bacteria gives them the aura of virtuous conquerors, driven by their will to protect their patients or vulnerable animals from the malfeasance of pathogenic bacteria. But, as such, this Manichean representation no longer holds in our current ecological situation, which completely disregards this romantic sanitary chivalry, and instead reminds us of the necessity to build a generalised, harmonised relationship to healthcare.

Less heroic, more cautious, the health practitioner of our day finds himself in a different role, which we must now define together, with at least two precautionary measures.

Firstly, let us consider that the practitioner’s responsibility must not be intensified, but broadened. Hence we will restrain from placing more pressure on the various actors of the medical body, focusing instead on a qualitative approach of healthcare.
Indeed the practitioner, no longer confined to the interpersonal aspect of his practice (the doctor/patient or veterinarian/animal relationship) within a short timespan, should consider his practice in a global and durable perspective.

If the matter of caregivers’ new responsibilities is a pressing one, it is precisely because of the responsibility they have been made to bear hitherto.
There lies the second - and no less important - point that requires caution, to which again the emblematic case of the phenomenon of antibiotic resistance testifies. As Jacques Fouad Acar pointed out with emphasis, here is another pitfall in the analysis of our helplessness in facing antibioresistance : the uncalled for search for scapegoats.

Misuse of antibiotics should not be construed as the sole cause of the adaptation of bacteria to their surroundings. In the microbiologist's words: ‘Medicine does not point fingers at anyone!’ Whether they be pointed at patients, doctors, livestock breeders, pharmacists, veterinarians, or any other, guilt-mongering constitutes a considerable misstep in apprehending the phenomenon of antibiotic resistance.

We speak of antibiotics in terms of logistics : ‘antibiotics stewardship’, when it is urgent to talk about the ethics of care, epistemology and about the definition of health.

As a result, these considerations lead to the necessity of acknowledging cultural, historical and symbolic variations in different representations of what health is, as well as a work of adaptation to these specificities.

If public health policies aiming at a standardisation of medical practices allow more coherence from a strategic viewpoint, they omit the irreducible diversity in representations of health, which remains an essential fact when considering the appropriation of the ‘One Health’ approach.

The ambitious international project ‘One Health’, which generates sincere emulation, depends precisely on our approach to subjects such as the phenomenon of antibiotic resistance, at the meeting point between societal issues, consideration for the invisible spectrum of the Living, and a holistic approach to healthcare.

Léonie Varobieff, Consultant, lecturer and expert in philosophy, specialist in ethics of health, care and ecology. She investigates the links between ecological stakes and sanitary crises, and questions the One Health approach, through studying the case of antibiotic resistance.
PhD student in philosophy - ANSES - CNRS IRPhiL laboratory Lyon III University, France

References

Andremont Antoine, Antibiotiques, le naufrage, Notre santé en danger, Bayard Culture, Paris, 2014.

Brives Charlotte, Que font les scientifiques lorsqu'ils ne sont pas naturalistes ?, Le cas des levuristes, in L'homme 2017/2 (n°222), p.35 à 56.

Coutellec Léo, Pour une philosophie politique des sciences impliquées, Valeurs, finalités, pratiques, in Ecologie et politiques, 2015/2 (n°51), p.15-25.

Ferdinand Malcom, Pour une écologie décoloniale, Paris, Seuil, 2019.

Pradeu Thomas, Philosophie de la biologie, in Barberousse, Bonnay & Cozic (eds.), Précis de philosophie des sciences, Paris, Vuibert, 2011.

Pierron Jean-Philippe, Vulnérabilité, Pour une philosophie du soin, PUF, 2010..

SCIENTIFIC ADVISORY COMMITTEE & TEAM* MEMBERS

A Research & Implementation Think-Do-Tank on Antimicrobial Resistance

Algeria UAE	**Nora Mahfouf***	PhD, University of Chadly Ben Djedid; Researcher Phages; consultant Arabic scientific publications, Dubai
Belgium	**Daniel De Vos**	PhD, Research Lead, Lab. for Molecular & Cellular Technology, Queen Astrid Military Hospital, Brussels
Benin	**Angèle Theodora Ahoyo**	PhD, Professor, Lab. Human Biology Eng, University Abomey-Calavi, National Focal Person Patient Safety, Cotonou.
Benin	**Bawa Boya***	PhD, Microbiology, Univ. Abomey Calvi, Cotonou
China	**Tong Zhang, Prof.**	PhD, Professor, Env. Biotechnology Laboratory, Dept. of Civil Engineering, The University of Hong Kong, Hong Kong
France	**Jacques Acar † decd.**	Founder AMR Think-Do-Tank, Geneva International, Prof., MD, Senior Expert to OIE, WHO-AGISAR and Fleming Fund; Founder and former President of ESCMID and ISID.
France	**Arno Germond***	PhD, Systems Biology & AI; Nat. Res. Institute for Agriculture, Food & Environment_INRAE, France; former Riken Labs, Japan, Vice-President AMR Think-Do-Tank, Geneva Int.
France	**Antoine Andremont**	Professor, MD, Emeritus Professor, University of Paris Medical School.
France	**Camille Méloux***	Health Care Worker, IPC Projects collaborator
France	**Fabienne Ostermeyer**	President, Foster Conseil Cie, Paris
France	**Jean-Jacques Monot***	MSc, Computer Systems Engineer, formerly Global Forum for Health Research, Health R&D financing statistics
France	**Marie-Paule Kieny**	MD, PhD, AMR R&D lead at INSERM, France, former ADG, WHO
France	**Pascal Simonet**	PhD, Professor, Research director, National Center for Scientific Research (CNRS), Member of Biotechnologies High Council (HCB)
Germany	**Dominique Thierry**	PharmD, Executive MBA, Global Director Quality, Hoya Surgical Optics, Frankfurt
India	**Abdul Ghafur**	MD, Coordinator, "Chennai Declaration on AMR", Apollo Hospital Hon. Adj Associate Prof. Ct in Inf. Diseases & Clinical Microbiology, Chennai
Ivory Coast	**Frank Mansour Adeoti**	MD, Africa Director, Int. Network for Planning & Improving Quality/Safety in Health Systems, Africa, INPIQS-RIPAQS, Abidjan
Japan	**Motoyuki Sugai**	PhD, Professor, Director, AMR Research Center, National Institute for Infectious Diseases, Tokyo
Japan	**Satoru Suzuki**	PhD, Professor, Env. Microbiology, CMES, Ehime University, Matsuyama
Mexico	**Mussaret Zaidi**	PhD, MD, Head, Inf. Diseases Research Unit, Hosp. General O'ran, Merida
Netherlands	**Laetitia van Haren**	MSc, President NGO SAHFA, Smart Access to Health for All
Netherlands Egypt	**Mostafa El Yamani***	MSc, Pharmacist & PhD candidate on AMR, Editor, Cairo & Maastricht
Nigeria France	**Lola Olawumi-Aye***	RN, Nurse, Nigeria
Scotland	**Susan Roaf**	PhD, Emeritus Prof., Architectural Engineering, Heriot Watt University, Edinburgh
Senegal	**Awa Aidara Kane**	PhD, Professor, Founder & Lead AGISAR WHO 2008-2019, Switzerland
South Africa	**Lyn E. Middleton**	PhD, Professor, College of Health Sciences, Kwa Zulu Natal University, Durban
South Africa	**Sabiha Essack**	PhD, Professor, Lead, AMR & One Health for the Rep. of South Africa & General Secretary, Academy of Science of the Rep. of South Africa

South Africa	**Precious M. Matsoso**	MA, MS, Member, Independant Panel on Pandemic Preparedness & Response, WHO; former DG, Health Services, South Africa, Director HRSP Division at University of Witwatersrand.
South Africa	**Vernon Solomon**	PhD, Professor, University of KZN, Durban
Spain Switzerland	**Jesús Rodríguez Baño**	MD, Professor, immediate Past-President, ESCMID, Switzerland; University of Medicine, Seville, Spain
Switzerland	**Aïssata Kagnassi***	MScF, University of Lausanne
Switzerland	**Catherine Fiankan-Bokonga**	UN Senior Correspondant, Vice-President, Association of Accredited Correspondents at the UN (ACANU)
Switzerland Italy	**Mario Raviglione**	Professor, MD, Director Global Health, University of Milan, Italy, former TB Director at WHO
Switzerland	**Meena N. Cherian**	MD, Director, Emergency & Surgical Care, Geneva Foundation for Medical Education & Research, GFMER, Advisor SIOD.
Switzerland	**Michaela Told**	PhD, Independant Consultant, former Director Global Health Center, IHEID,
Switzerland	**Mwai Makoka**	MD, Programme Executive for Health and Healing, World Council of Churches, Geneva
Uganda	**Jane Kegeya-Kayondo**	PhD, Currently Founder & CEO of ROUTE, a non-profit Skilling Young Adults In Africa with Employability, Business and Life Skills. Former Wellcome Trust special adviser for Africa, and ex-TDR/WHO.
United Arab Emirates	**Elias Tannous**	MBA, BSN, CIC, Founder Arab Countries Infection control Network (ACICN), & IPC, Abu Dhabi
United Kingdom	**Emma Hayhurst**	Senior Lecturer in Microbiology, UK Water Industry Research, lead on AMR in waste and drinking water, South Wales
United Kingdom Switzerland	**Manjit Dosanjh**	PhD, Visiting Prof, Oxford University, UK; Member ICEC (Int. Cancer Expert Corps). CERN Senior Advisor for Medical Applications, Geneva. Founder: Smart Technologies to Extend Lives with Linear Accelerators
USA	**Cassandra Leah Quave**	PhD, Professor. of Dermatology, Director Herborarium, Emory University School of Medicine, Atlanta
USA India	**Chandra Pauline Dinakar Daniel**	PhD, UN Association Global Goals Ambassador, DrPH Health Policy and Management Program, N.Y. Medical College, formerly NABLA. NYC.
USA France	**Garance F. Upham***	MSc; Member R&D Working Group, SE Asia; former Vice-President, WAAAR; former St. Ctte Patient Safety WHO, Stk Mb, Global AMR R&D Hub. Founder & President, AMR Think-Do-Tank Geneva Int.
USA	**Lisa Dolan-Branton**	RN/BSN, Technical Director Afghanistan & India MNCH/IPC, ex-URC Senior Improvement Advisor Africa, Middle East IPC/ Malaria
USA	**Padmashree Gehl Sampath**	PhD, Fellow & Senior Advisor, Global Access in Action Program, Berkman Klein Center, Harvard University, formerly UNCTAD, WHO, UN, Boston
USA	**Steffanie Strathdee**	PhD, Professor, Co-Director IPATH, Associate Dean of Global Health Sciences, Univ. of California San Diego UCSD

Note: affiliation for ID purposes only. The Scientific Advisory Committee is a consultative body, the majority of its members are women, many of whom have had, or still have, key tasks in AMR and One Health, and most do LMIC field work.

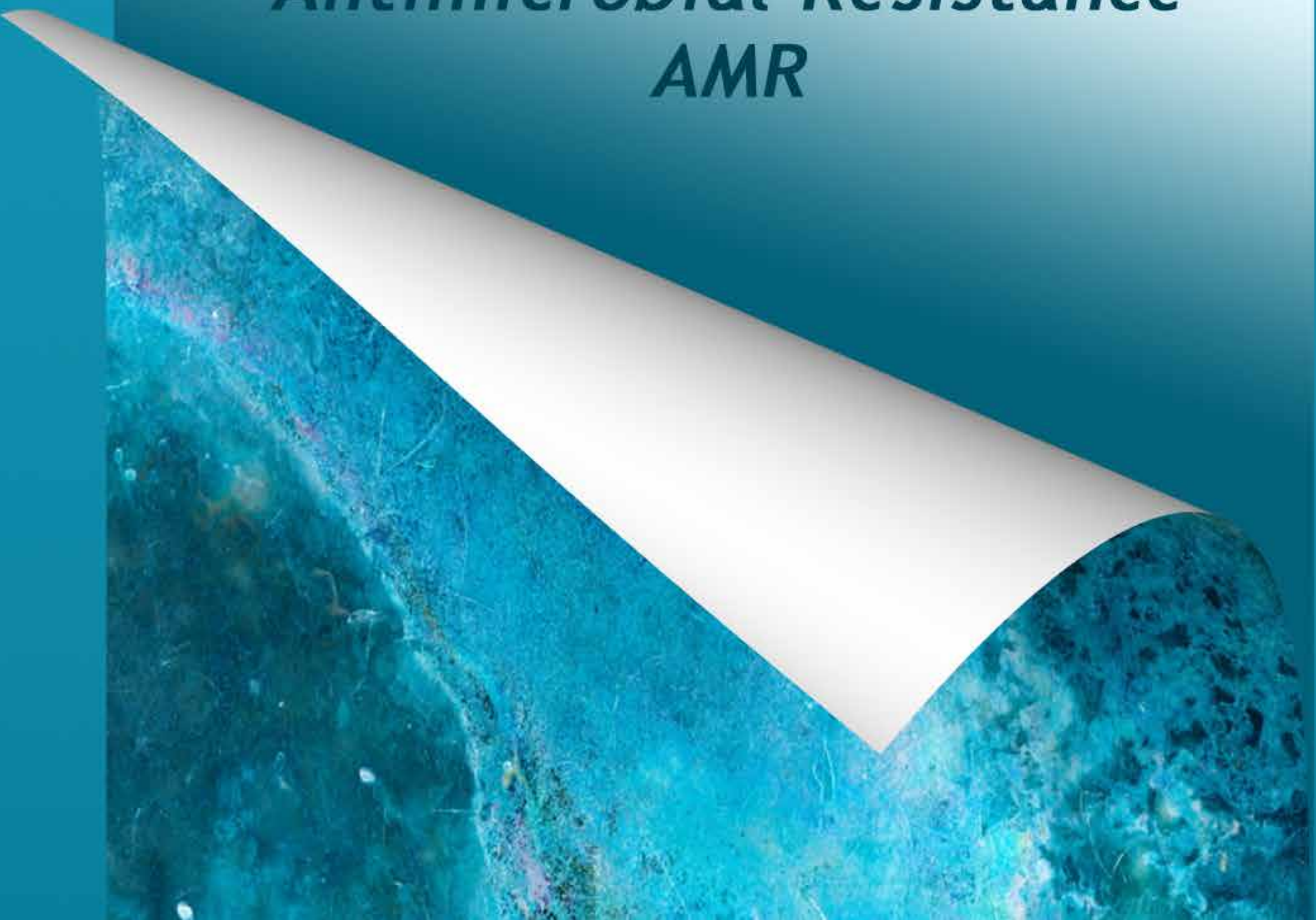
Disclaimer: *The designations employed and the presentation of the material in this publication* "**AMR & The Environment, a Global and One Health Security Issue**" *do not imply the expression of any opinion whatsoever on the part of the AMR Think-Do-Tank Geneva Int. and its Scientific Advisory Committee Members, the named authors alone are responsible for the views herein expressed.*

A Research and Implementation Think-Do-Tank on AMR, it brings together a global multidisciplinary scientific task force. The purpose is to bring in different bodies of expertise, and multiple points of views, to examine possible approaches to the many faceted aspects of AMR infections: prevention in and out of health care settings, environmental origins and determinants of AMR, economics and financing of related AMR/One Health issues. Researchers, nurses, doctors, engineers, economists, anthropologists, health care workers, innovators, philosophers, all welcome.

"It ain't what you don't know that gets you in trouble. It's what you know for sure, that just ain't so." Mark Twain

THINK-DO-TANK AMR GENEVA INTERNATIONAL

A Research and Implementation Think-Do-Tank on Antimicrobial Resistance AMR

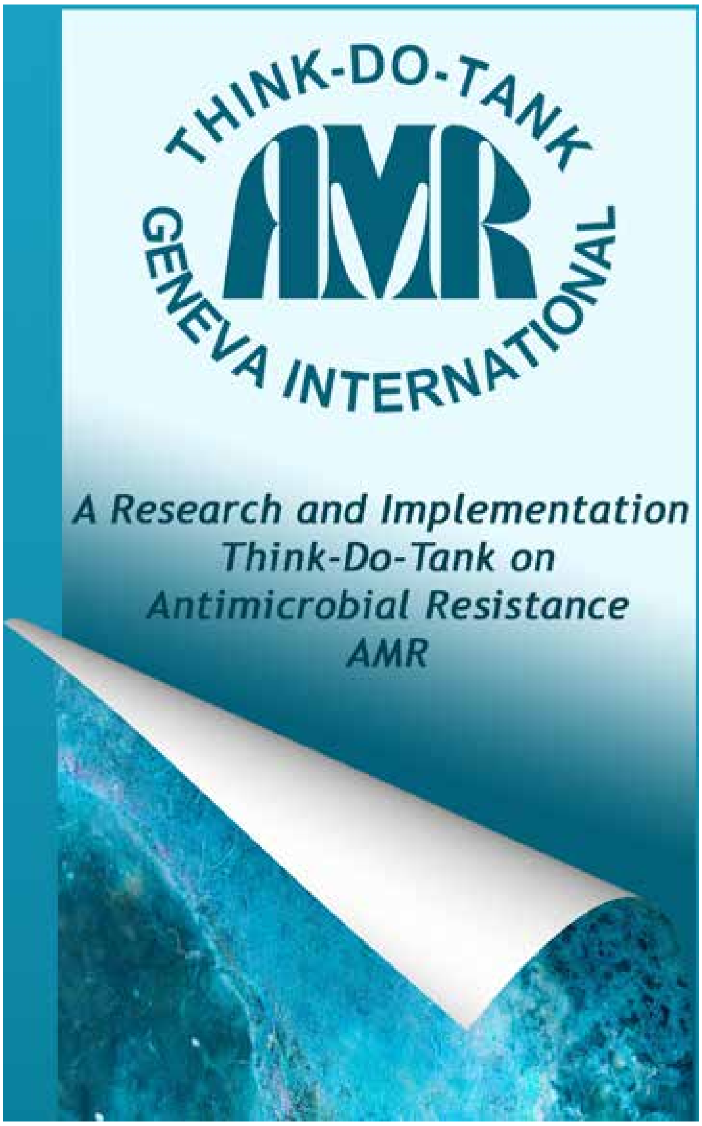


AMR & THE ENVIRONMENT

A Global & One Health Security Issue

Director of Publication & Editor in Chief:
Garance F. Upham

A publication of the AMR Think-Do-Tank, Geneva International
Maisson des Associations, Rue des Savoises 15,
1205 Geneva, Switzerland



Obituary : Jacques F. Acar (1931-2020)

What's exciting about a Think Tank?

Section I - The Environment:
From Surveillance to Solutions
AMR & SARS-CoV-2
Benin, China, France, United Kingdom.

Section II - AMR in Aquaculture. Japan.

Section III - AMR Fungal Infections. Australia.

Section IV - COVID-19 & AMR:
IPC & Airborne Disease Spread. China, Portugal, Saudi Arabia, Scotland, WHO-EMRO.

Section V - Global Health Security &
Economic Policy Debate. Australia, USA.

Section VI - Improving Care Quality & Access:
From Infections to NCDs.
Botswana-Switzerland-United Kingdom;
United Arab Emirates; Netherlands/Afrique.

Section VII - Conclusions:
One Health Vs Global Health. France.
The Scientific Advisory Committee

www.amrthinkdotank.org

email: info@amrthinkdotank.org

ISSN 2673-9232

132 pages; glossy paper, A4 format
Price: 79 CHF / 69 euros
Reduced prices for LMICs - email us