APPROPRIATE USE OF ANTIMICROBIALS: A CURRENT CHALLENGE

Online seminar. September 18th, 2020

REPORT

The Global Health Consortium at the Robert Stempel College of Public Health and Social Work, Florida International University GHC@FIU, in partnership with the Pan American Health Organization (PAHO) organized an online seminar on the current challenge of the adequate use of ATB, on Friday, September 18th (9:30 am – 12:00 pm ET).

Developed jointly by Dr. Dr. Pilar Ramón-Pardo, Team Lead, Antimicrobial Resistance Special Program, Communicable Diseases and Environmental Determinants of Health, PAHO WHO and Dr. Carlos Espinal (Director, GHC@FIU), the online seminar was part of the strategic program designed by the GHC@FIU and PAHO aimed at mitigating the impact of antimicrobial resistance (AMR) in the region.

Invited speakers were Dr. Ingrid Smith, from WHO Geneva, Dr. Valeria Fabré, from John Hopkins University, Baltimore, USA, Dr. Marcio Borges, from the Panamerican-Iberian Federation of Critical Medicine and Intensive Care, Spain and Dr. Rodolfo Quirós from Argentina, currently Executive Director the Angel Foianini Clinic in Santa Cruz de la Sierra, Bolivia. Dr. Pilar Ramón-Pardo was also a speaker at the online seminar. Dr. Espinal co-chaired the panel discussion and questions from the audience with Dr. María Virginia Villegas, an expert in Infectious Diseases with a Masters' degree in Tuberculosis, currently the Executive Director of the International Center for Medical Research and Training in Colombia.

Introduction

Dr. Ramón-Pardo and Dr. Espinal set the goals of the online seminar: to analyze the current situation and the impact of the SARS-CoV-2 pandemic in the use of AM agents, to name the main challenges and to look for innovative strategies for the control and prevention of antimicrobial resistance (AMR), in the COVID-19 era.

New WHO interim guidance on ATB use in COVID-19.

Ingrid Smith, WHO, Genève

A study by Huttner et al.: "COVID-19: don't neglect AM stewardship principles" states that an important proportion of patients with COVID-19 present with fever and cough, and those requiring hospitalization because of dyspnea usually present bilateral radiological infiltrates. The authors have a good quote which sums up the situation across the globe when it comes to COVID-19 and antibiotic (ATB) use: "Despite the viral origin of COVID-19, a standard reflex by physicians is to start treatment with ATB, since cough, fever and radiological infiltrates are hallmarks of bacterial community-acquired pneumonia (CAP) which requires ATB treatment. The anxiety and uncertainty surrounding the pandemic and the absence of antiviral treatments with proven efficacy are probably other contributors to the widespread and excessive prescription of ATB."

Another key issue in this publication, which will probably be part of the discussion today in the online seminar, points out certain issues that are important to remember, in response to a pandemic:

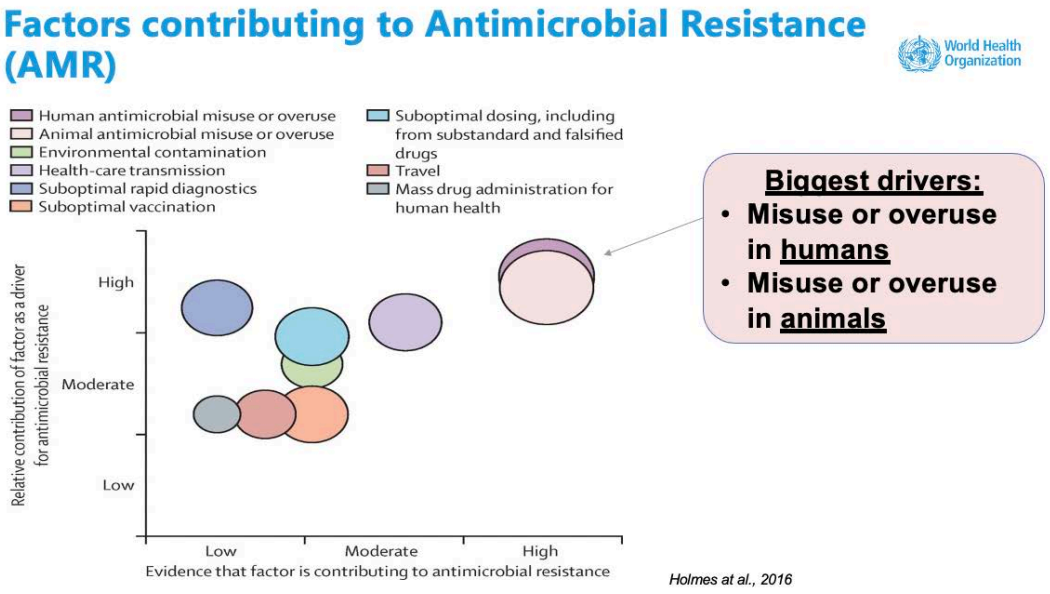
Table 1
Research needs regarding COVID-19 and antibiotic steward

Research need	Study design	Challenges	Comment
(1) Establish the exact incidence of bacterial co-infection and superinfection at the different phases of the disease	Observational cohort study or in the context of randomized controlled trials assessing other interventions	Adequate diagnostics of lower respiratory tract infections require bronchoalveolar lavage (BAL) which may be difficult to perform (risk of respiratory deterioration, risk of exposure for healthcare personnel, resource constraints) Limited availability of bacteriological tests in the context of the pandemic)	• Ideally combined with (2)
(2) Assess the diagnostic performance of biomarkers to rule out/rule in bacterial superinfection	Observational cohort study or in the context of randomized controlled trials assessing other interventions	The reference standard (presence or absence of bacterial super-/co-infection) may be difficult to ascertain and may have suboptimal accuracy by itself: see (1)	• Ideally combined with (1) • Ideally studies should assess more than one biomarker
(3) Better understand the contribution of infection versus immune response in the different phases of COVID (first days after start of symptoms versus second week)	Observational cohort study or in the context of randomized controlled trials (e.g. of immune-modulating interventions such as steroids or IL-6 or IL-1 inhibitors)	See (1). Obtaining BAL samples may be challenging	
(4) Assess the impact of the COVID pandemic on antibiotic use and resistance in all settings (community, nursing homes, hospitals)	National, regional, local surveillance of antibiotic use and resistance based on established networks	Many confounding factors besides antibiotic use need to be taken into account (e.g. overcrowding of hospitals)	

Several systematic reviews on bacterial infections (Lansbury *et al., Journal of Infection* May 2020; Rawson et al., *CID* May 2020; Clancy C J and Nguyen MH. *CID* May 2020) show that many COVID-19

patients (~72%) receive broad-spectrum ATB, whilst the incidence of bacterial infection is low, even lower than for influenza.

It is extremely important to optimize ATB treatment during the pandemic, since misuse / overuse of ATB both in humans and in animals is the major driver of AMR.



There are risks and opportunities for AMR and achieving universal health coverage (UHC). AMR is a threat to effective UHC, so addressing AMR supports health systems strengthening.

Challenges of AMR to health systems strengthening:

- Higher mortality and morbidity
- More difficult to treat infections
- Longer hospital stays
- Need for more costly treatment
- Up to 25% increase in health-care costs in low-income countries
- Heavy burden on health systems

Addressing AMR is core for strengthening health systems:

- Resilient health system to prevent, diagnose and manage infections
- Clean and safe health facilities

- Optimize use of ATB
- Health workforce that understands and appropriately manages AMR risks
- Effective collaboration with other sectors

AM stewardship is a very difficult term. In Spanish it has been translated as “programs to optimize AM use”. The actual definition, objectives and action of AM stewardship programs (ASP) is a “coherent set of actions to promote using AM responsibly” with the ultimate goals of:

- Changing prescribing practices of ATB
- Optimizing ATB use; treatment/ prophylaxis
- Extending the lifespan of existing ATB; so that they are still effective
- Reducing the development of AMR
- Improving the quality of healthcare
- Saving patients’ lives and health-care costs

It is essential not to prescribe/use ATB when not needed, to use the *older* ATB when they are sufficient for treating the infection and reserve the n*ewer* ATB to be used exclusively when needed. COVID-19 offers opportunities to advance implementation of ASP, including improving ATB prescribing:

Nine common areas for improving antibiotic prescribing

PRESCRIPTIONS	WHAT TO IMPROVE
1. Overprescribing	Antibiotics are prescribed when not needed, e.g. fever without evidence of infection, asymptomatic urinary tract colonization, viral infections, malaria, inflammatory conditions.
2. Overly broad spectrum	More broad-spectrum antibiotics (WATCH and RESERVE antibiotics) are prescribed than are necessary (e.g. surgical prophylaxis).
3. Unnecessary combination therapy, including certain fixed-dose combinations	Multiple antibiotics are used, particularly with overlapping spectra and in combinations that have not been shown to improve clinical outcomes.
4. Wrong antibiotic choice	Wrong antibiotic(s) are prescribed for particular indications/infections.
5. Wrong dose	Antibiotics are prescribed with the wrong dose (over- or underdosing).
6. Wrong dose interval	Antibiotics are prescribed with the wrong dose interval (too much time between doses).
7. Wrong route	Antibiotics are prescribed by the wrong route (e.g. IV instead of oral).
8. Wrong duration	Duration of antibiotic treatment should be optimized (e.g. antibiotics prescribed for too long a period, prolonged surgical prophylaxis).
9. Delayed administration	Administration of the antibiotic(s) is delayed from the time of prescription. Repeat doses are not administered in a timely way, which is critical in the case of septic shock and other serious infections.

To try and promote a more optimal use of ATBs during the COVID-19 pandemic, the AM stewardship team in WHO took part in developing the Clinical management guidelines of COVID-19. In this document, AM stewardship guidelines were provided, as well as ATB treatment recommendations:

We recommend against antibiotic therapy or prophylaxis for patients with mild COVID-19.

Remark:

Widespread use of antibiotics should be discouraged, as their use may lead to higher bacterial resistance rates, which will impact the burden of disease and deaths in a population during the COVID-19 pandemic and beyond *(73, 74)*.

We recommend for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection.

suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors and local epidemiology, and this should be done as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation.

epidemiology and susceptibility data, and national treatment guidelines. Choose antibiotics with the least ecologic impact based on data and guidance from your own institution, region or country (e.g. of the Access group of the AWaRe classification) *(76)*.

The Guidelines also provide some recommendations on how to prevent complications of COVID-19, such as how to reduce the incidence of ventilator-associated pneumonia or catheter-related bloodstream infections. Preventing this type of infections will also influence the use of ATBs in COVID-19.

Prevention of complications of COVID-19 illness

World Health Organization

Table 3. Prevention of complications

Anticipated outcome	Interventions
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30–45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed

18

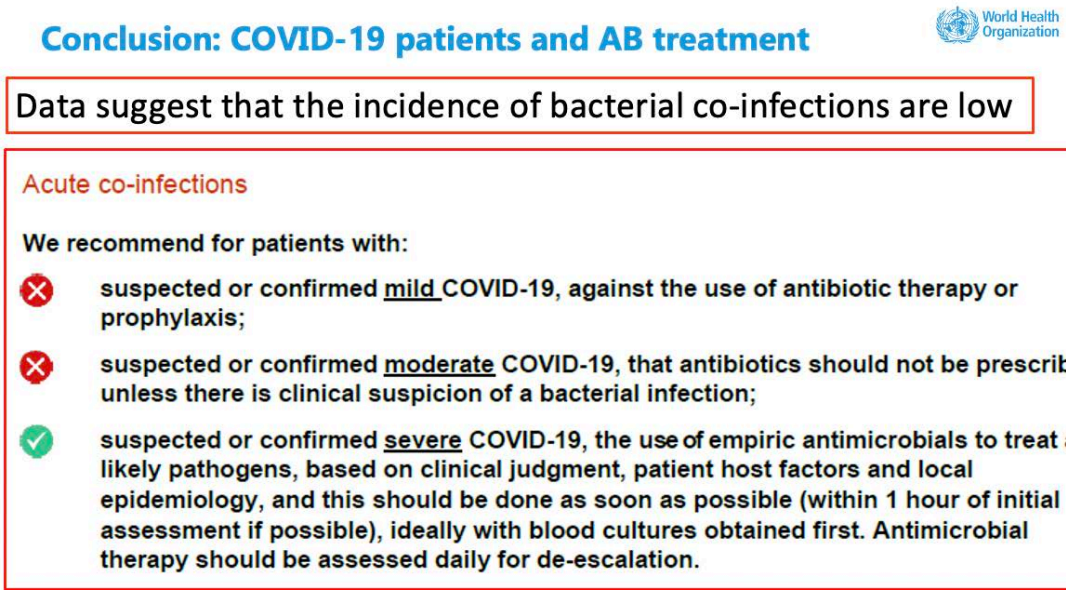
Prevention of complications of COVID-19 illness

World Health Organization

Table 3. Prevention of complications

Anticipated outcome	Interventions
Reduce the development of antimicrobial resistance	• Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection
Reduce the development of adverse drug effects	• Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use
Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic *(121)*	• Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance

In order to provide these recommendations, it was very important that we actually had information about the incidence of bacterial co-infections. Many papers show that the incidence is low. In conclusion, these are the recommendations for ATB treatment in COVID-19 patients:



AM optimization programs and containment of AM resistance. Perspective from Latin America and the Caribbean.

Pilar Ramón-Pardo, OPS, Washington, D.C.

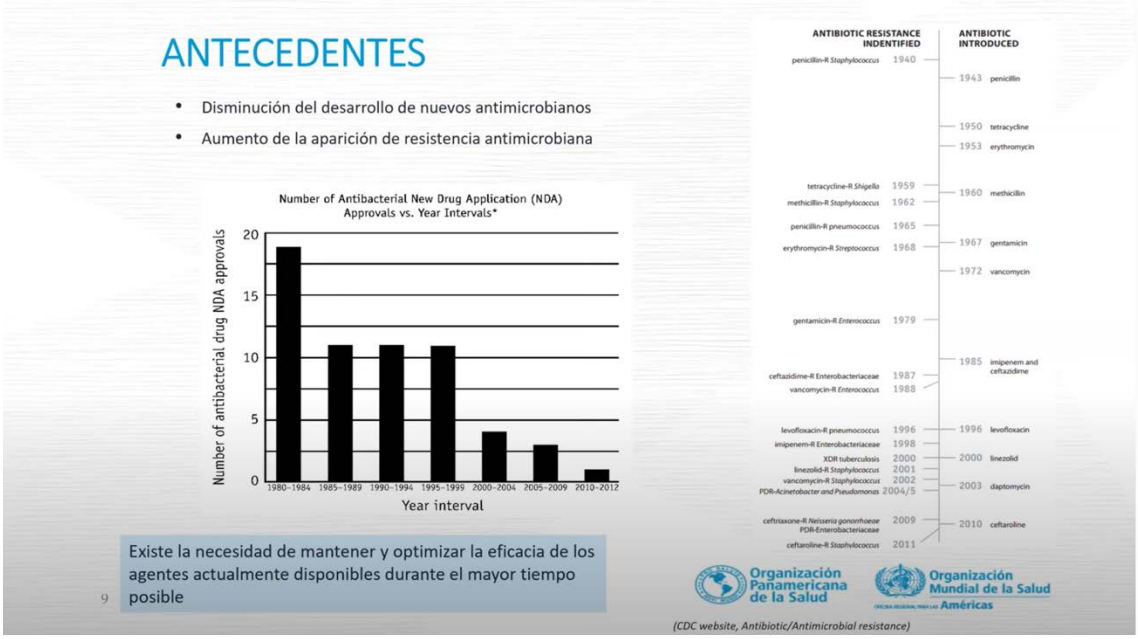
I will present an overview of the recommendations from the Pan-American Health Organization/World Health Organization (PAHO/WHO).

The inappropriate or excessive use of AM is a problem more relevant than ever that requires a coordinated response. In the context of the COVID-19 pandemic in the region of the Americas we have almost half of the cases globally, and more than half of the deaths. This means that the pandemic is impacting very strongly in our countries. Patients that are mainly entered in intensive care have a greater vulnerability for bacterial infections because they have associated underlying diseases and risk factors, they are under corticosteroid therapy, have respiratory diseases, and are undergoing invasive procedures. It has also been documented that bacterial infections are related to COVID-19, and that a considerable number of deaths in COVID-19 patients is related with bacterial infections. However, this number of infections is much smaller than the percentage of patients who are receiving AM in relation with COVID-19 (10%-15% vs. 94%-100%). It is very possible that there is an improper use of AM.

We also know that the overload of health services is going to have an impact on health care associated infections that will probably depend on each health care facility, despite the pandemic has led us to strengthen the infection control practices, the proper use of personal protective equipment, the standard contact precautions, etc.

The improper use or the overuse of AM both in humans as in animals is the factor that most contributes to AMR, we have not yet measured the increase due to COVID-19, but we already know that it exists, so we will see an increase in AMR.

This slide shows the severe problem of the decrease in the number of new molecules being developed.



WHO has classified the list of essential medicines into three large groups depending mostly on their ecological impact. The reserve group includes those AM with the largest spectrum, only to be used in specific circumstances.

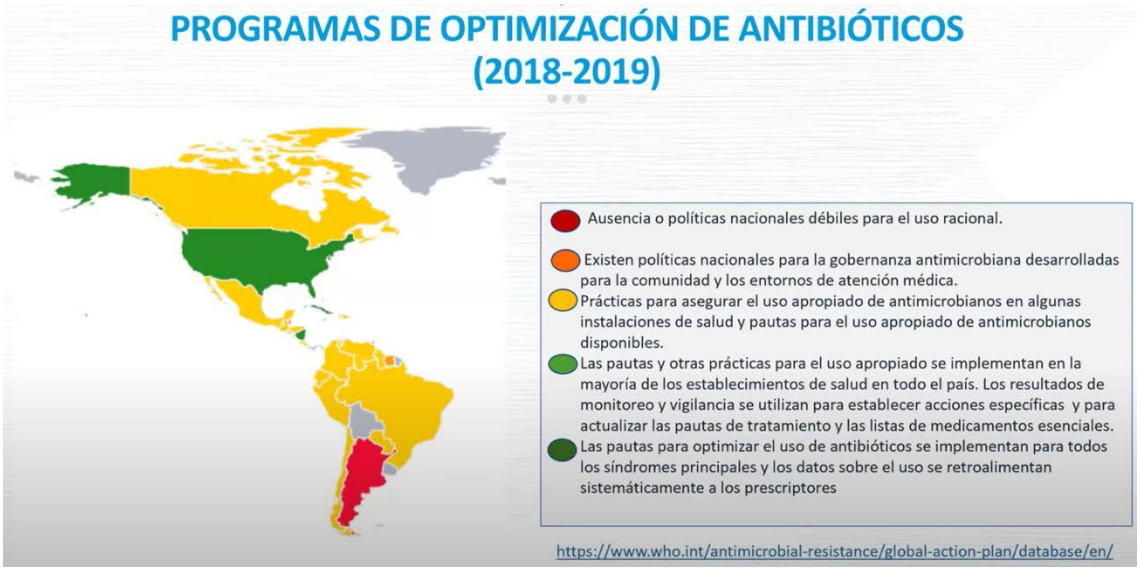
Between 2015 and 2050, 2.4 million people will die in Europe, North America, and Australia due to AMR; 75% of these deaths can be avoided by investing U$S 2 per person/year. It is of course a significant amount, but the return is important. The cost of these policies would be recovered in just one year.

One of the most effective measures, besides hand hygiene, are ASPs, the most cost effective and the one with most impact on reducing mortality. ASPs have shown to reduce infection and colonization by hospital pathogens, both gram-negative bacteria and gram positive such as *Staphylococcus aureus*, and they have also shown to decrease the incidence of infections due to *Clostridium difficile*. Another benefit is that they decrease the use and the cost of broad-spectrum ATB, which are at the highest risk of developing AMR. ASPs also impact on the quality of health care services, by using more appropriate AM therapy, with subsequent less therapeutic failure and less AMR.

Today, most countries in the Americas have national action plans against AMR, in line with the strategic global action plan:

1. Improve awareness and understanding
2. Surveillance and research
3. Reduce the incidence of infections
4. Optimize the use of AM, and
5. Ensure a sustainable investment

This map shows how countries in the Americas have been progressing in implementing these plans (data as of 2018-2019).



Most of the countries are in the yellow stage, i.e., they are on the way but still need a little more momentum to implement their ASPs and monitor their impact, but the general picture shows that the region is on the road of setting these ASPs. Monitoring of the use of AM is part of these programs; when performed at a national level important data is obtained, allowing to see not only how much is consumed but in which categories.

WHO has developed a survey on the prevalence point on the use of AM, which has been implemented in Latin America and the Caribbean, allowing to monitor AM prescription rates in hospitalized patients. Based on the results, countries will identify areas to improve, develop tailored interventions and evaluate their efficacy.

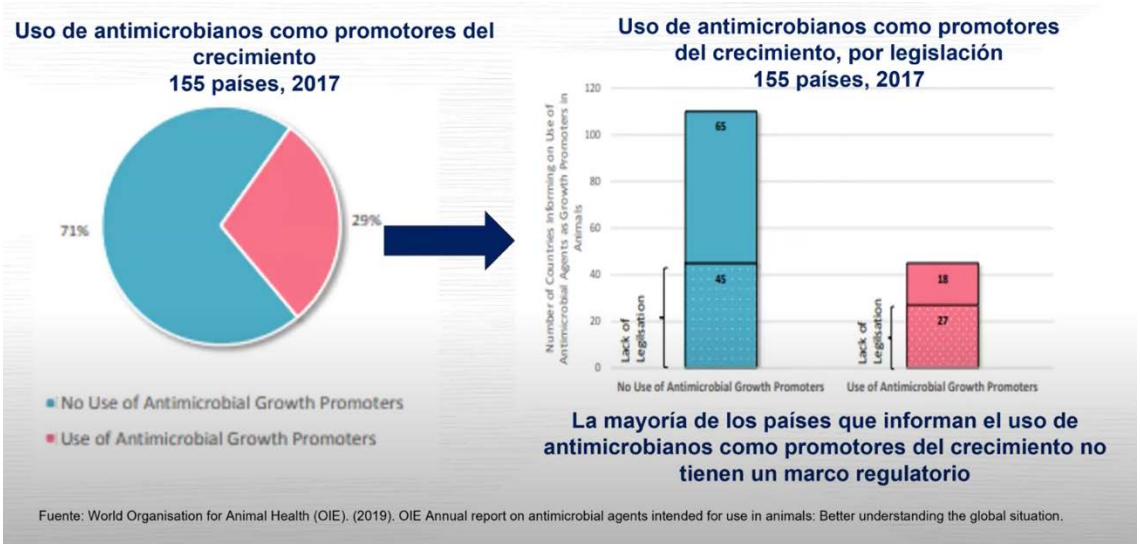
The experience we have completed in the Caribbean shows that each country and each institution have a different profile in the use of AM, and it is important to know what is being used in each hospital, in which circumstances, where improvement is needed, and target the interventions.

There are challenges to implement PROAS in limited resources settings, such as the lack of protocols or updated treatment guides, the lack of specific training for specialists in infectious diseases and hospital pharmacy, there is a great shortage in the region in microbiological diagnosis, as well as limited human

resources and sometimes there is difficulty in obtaining institutional and financial support to implement these programs.

There are some tools that can help address these challenges, such as the recommendations for implementing ASPs developed jointly with FIU, guides prepared by the Latin-American association of Infectious Diseases, and a small manual by PAHO, in its 8th edition, recommending AM treatment according to AMR prevalence.

Regarding AMR related to veterinary sciences, the World Organization for Animal Health (OIE) is working on AM consumption in animals, monitoring the field of veterinary medicine and food production.



This slide shows that there is still a challenge in controlling the use of AM as growth promoters. Almost a third of the countries completed the 2017 survey and although they are improving, they are still lacking legislation.

The rational use of ATB in hospitals improves quality care and contributes to the control of resistance. This is extremely relevant in the time of COVID-19, with the increase in hospital and in ICU admissions.

The call to attention message is also directed to other sectors also responsible of AMR, so it is important that countries have a comprehensive multisectoral view to address this issue.

HCP training is key to achieving the appropriate use of AM.

Bacterial coinfections and use of ATB in patients with COVID-19.

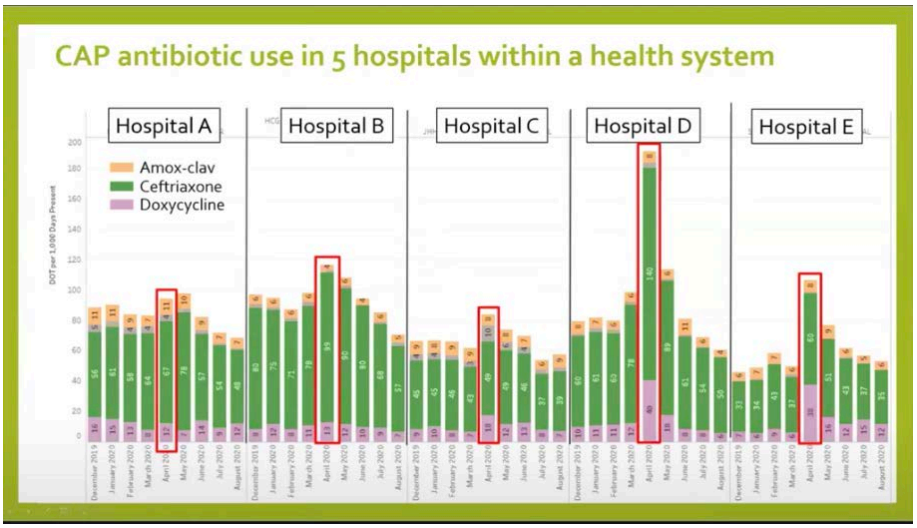
Valeria Fabré, John Hopkins University, Baltimore, EUA

The goals of this presentation are to review some of the studies that have investigated the presence of bacterial and bacterial co-infections in patients with COVID-19, to talk about using ATB in these patients, to propose some strategies to reduce the use of ATB and to share recommendations on the use of ATB in patients with COVID-19.

One of the first studies that evaluated this issue is a British study by Adler et al. that included 195 patients with COVID-19 19 and reported a 5% prevalence of pneumococcal co-infection (based on blood/sputum culture or urine antigen). Lansbury et al in a meta-analysis including a much larger sample, with over 3,800 patients and mainly retrospective observational studies from patients in China, the pooled proportion of bacterial co-infection in patients with COVID-19 19 was 7%. The main pathogens found were *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Klebsiella pneumoniae*. The limitations of this meta-analysis were not to have full information on the timing of co-infection, incomplete data on pathogens involved, and heterogeneity in defining co-infection.

In a literature review, Rawson et al. included 9 studies on COVID-19 with 407 patients from China and 359 from USA and reported a similar prevalence to the previous one (8%). Most recently, Vaughn et al. published a multicentric cohort study on empiric AM treatment in patients with COVID-19 and community acquired bacterial co-infection. The study is based in the state of Michigan and includes 1,705 patients randomly selected in 38 hospitals. The incidence of a confirmed community-onset bacterial infection was 3.5 %; 60% of the patients admitted with COVID-19 in these hospitals received ATB for the first two days but it is important to emphasize that only a minority of these patients (22%) continued therapy once the positive result of COVID-19 is confirmed.

This slide shows the use of some ATB for the treatment of CAP in Maryland's health system.



Treatment duration is shown per 1,000 days/patients in each month (from Dec. 2019 through August 2020) in the 5 hospitals. The featured box is the month of April which is where COVID-19 peak occurred in Maryland, each color represents an ATB: amoxicillin-clavulanic / ceftriaxone and doxycycline. It is interesting to note the variation in ATB use in the different hospitals, which have different geographic locations and populations, e.g., D and E are two community hospitals and receive a much larger proportion of patients from nursing homes. Although during the COVID-19 peak month an increase in the use of ATB for CAPis clearly seen in each of these hospitals, it is encouraging to see consistently in all hospitals a decreasing use of ATB over time.

This slide summarizes the challenges associated with ATB decisions in COVID-19 infection:

Challenges associated with antibiotic decisions in COVID-19 infection

- Symptoms of viral pneumonia overlap with those of bacterial pneumonia
- Unfamiliarity of bacterial co-infections with an emergent pathogen
  - Pandemic H1N1 flu in 2009, bacterial co-infections affected 25% of cases
  - Main pathogens included *S. pneumoniae*, *S. pyogenes* and *S. aureus*
  - Was a contributor to mortality
- Patients with COVID-19 who meet sepsis criteria (specially residents from long-term care facilities)

ATB stewardship during COVID-19 faces different problems. One is the shift in the focus and dynamics of the team activities, both the doctor and the pharmacist, even reaching the point of lacking time to review literature and to stop MRSA surveillance.

Some of the solutions implemented rapidly during the pandemic was to focus on education where it was highly needed (as informed in the chart on AM use, shown before), promoting an open inter hospital dialogue, with a particular emphasis on reviewing ATB on day 2 and treatment duration. We were lucky enough to have a group of doctors who were not on duty and they could join a task force to review the literature and help develop treatment recommendations.

ATB are not recommended for treatment or prevention of bacterial pneumonia in patients with mild or moderate COVID-19. In community patients with suspicion of bacterial co-infection, non-broad-spectrum ATB should be used. ATB may be considered for severely ill patients, with the appropriate cultures before treatment start and de-escalating based on laboratory results.

There is robust evidence that 5 days is as effective as longer durations to treat community acquired pneumonia. One study even showed that 3 days was non-inferior to eight days for patients with mild to moderate CAP. Longer therapies should be considered for patients with slow or no clinical response within the first 72 hours, as well as for immunocompromised patients. Other indications are patients with underlying lung comorbidities and those who have had an inappropriate initial therapy.

We do not use procalcitonin but know that some hospitals do. There is limited data showing that procalcitonin may be increased in patients with COVID-19 who do not have evidence of a bacterial co-infection, especially if they have severe disease or are in the ICU. Elevated procalcitonin is seen in patients with cytokine storm syndrome and has also been associated with disease severity.

Despite the limitations of the studies to date, the data consistently shows that bacterial infections are an uncommon complication in COVID-19. ATB use may improve as the pandemic evolves, and clinicians are more comfortable managing COVID-19 patients.

Challenges in the care of COVID-19 patients in the context of a PROA.

Rodolfo Quirós, Clínica Ángel Foianini, Santa Cruz de la Sierra, Bolivia

This talk will cover the collateral impact of the pandemic on ASPs, the recommendations on the use of AM in the context of COVID-19, the challenges for implementation and sustaining these programs, how to adapt them to this new scenario, and the experience in a tertiary level setting.

As it has already been discussed in the preceding presentations, there was an increase in the use of AM (between 50% - 95%) in a short period of time and this is basically due to the empirical use of ATB in the initial management of COVID-19 pneumonia, and the use of azithromycin and antivirals with not enough evidence.

Another aspect of collateral impact of the pandemic in the context of stewardship is that their members had to change their roles and be appointed to direct patient care, there was also a reduction in health personnel either because some acquired COVID-19 and others showed burn out syndrome due to the heavy work load.

The rapid increase in telemedicine may also result in increased use of ATB. As what regards the laboratory, the demand of SARS-CoV-2 diagnosis reduced the time to process samples for common infections.

A study by Yixin Liew on ASP as a vital resource for hospitals during the pandemic, compared the consumption of ATB used for the treatment of CAP pre-COVID disease and during COVID, showing that the defined daily doses of ATB were higher during the onset of the pandemic, and how ASP interventions impacted on the median duration of ATB therapy and median length of stay after the program intervention.

Antimicrobial stewardship programme: a vital resource for hospitals during the global outbreak of coronavirus disease 2019 (COVID-19) Int J Antimic Agents 2020; https://doi.org/10. 1016/j.ijantimicag.2020.106145

Yixin Liew, Winnie Hui Ling Lee, Lunyi Tan, Andrea Lay Hoon Kwa, Siew Yee Thien, Benjamin Pei Zhi Cherng, Shimin Jasmine Chung

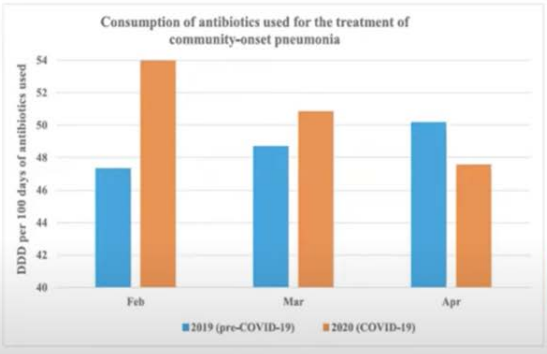


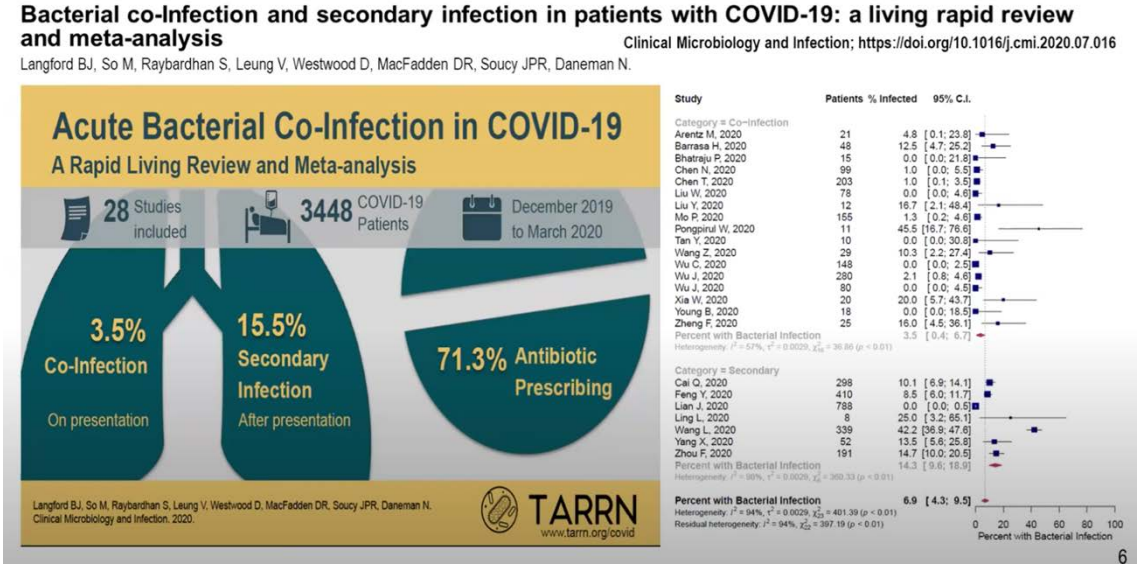
Fig. 1. Comparison of the consumption of antibiotics used for the treatment of community-onset pneumonia pre-coronavirus disease 2019 (COVID-19) (blue bars) and during COVID-19 (orange bars). Defined daily doses (DDD) of antibiotics (ceftriaxone, co-amoxiclav, levofloxacin, moxifloxacin, azithromycin and clarithromycin) were higher in February and March during the onset of the COVID-19 pandemic.

Table 1
Comparison of antibiotic stewardship programme (ASP) interventions and outcomes pre-coronavirus disease 2019 (pre-COVID-19) (1 February–30 April 2019) and during the acceleration phase of the COVID-19 pandemic (1 February–30 April 2020)

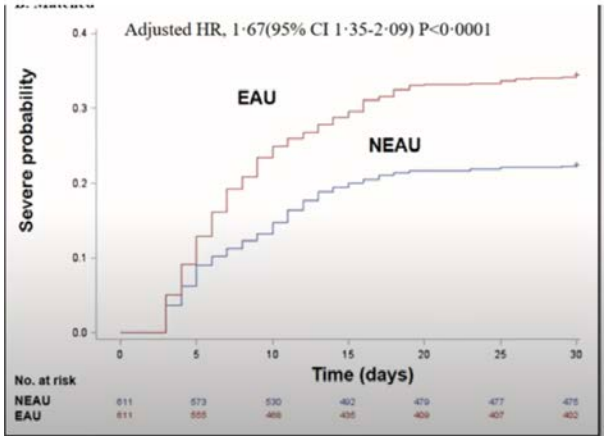
Types of interventions	pre-COVID-19[a], *n* (%) *n*=560			COVID-19[b], *n* (%) *n*=578		*P*-value
ASP acceptance	470 (83.9)			488 (84.4)		0.89
Type of ASP interventions						
Broaden empirical coverage	6 (1.1)			9 (1.6)		0.87
Narrow empirical coverage	102 (18.2)			102 (17.6)		1.00
Revision of antibiotics based on culture data	89 (15.9)			73 (12.6)		1.00
Discontinuation of antibiotics	217 (38.8)			181 (31.3)		0.69
IV to PO switch	64 (11.4)			79 (13.7)		0.49
Optimization of antibiotic doses	24 (4.3)			71 (12.3)		0.56
Trigger ID consult or ID review	35 (6.3)			30 (5.2)		0.11
Additional recommendations[c]	23 (4.1)			33 (5.7)		0.70
Impact of ASP interventions	Accepted	Rejected	*P*-value	Accepted	Rejected	*P*-value
Median duration of antibiotic therapy (IQR), days	3 (2–5)	6 (4–10)	<0.05[d]	4 (2–4)	8 (3.0 – 9)	<0.05[d]
Median LOS after ASP intervention (IQR), days	6 (2–15)	7 (4–11)	0.53	7 (4–16)	12 (7–28)	<0.01[d]

IV, intravenous; PO, per oral; IQR, interquartile range; LOS, length of stay; ID, infectious diseases.
[a] pre-COVID-19: this refers to the period between 1 February and 30 April 2019.
[b] COVID-19: this refers to the period between 1 February and 30 April 2020.
[c] Recommendations for diagnostic investigations and/or infection control precautions were made to guide management of the ID issues.
[d] *P*<0.05 was taken to indicate statistical significance.

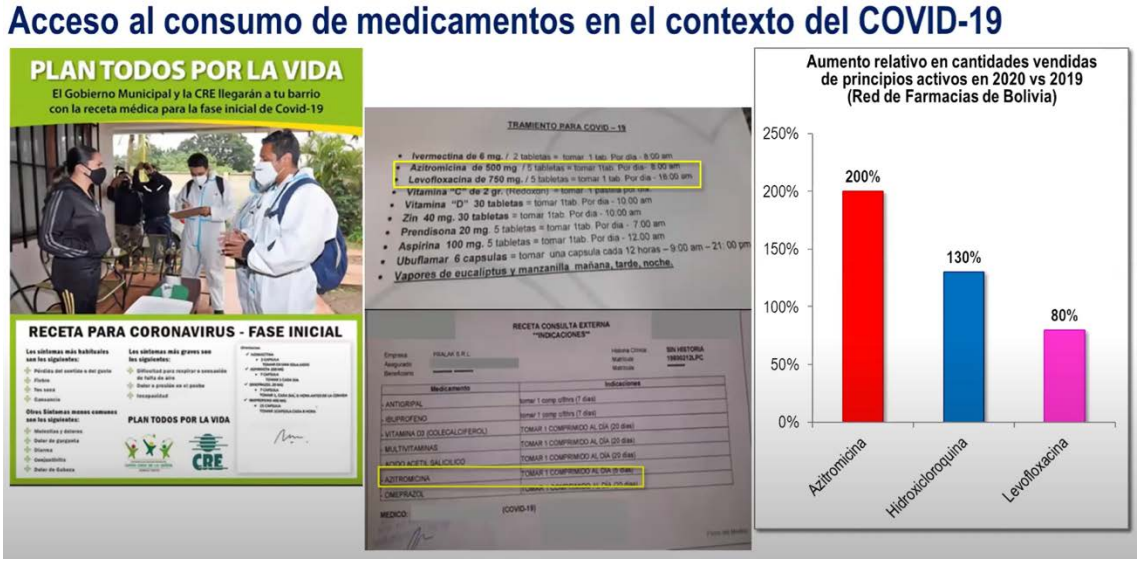
Langford BJ t al. rapid review and meta-analysis on the use of AM in bacterial co-infection and secondary infection in patients with COVID-19, in 28 studies with 3,448 COVID-19 patients, found that only 3,5% of patients had co-infection at the time of hospitalization, while secondary infection was found in 15,5% of the patients after hospitalization. ATB were prescribed in 71,3% of the cases.



Finally, an interesting study by Xiaoxv et al. evaluated the effect of early ATB use in non-severe COVID-19 patients admitted with low risk of bacterial infection, in 1,613 patients of which 996 received ATB within 48 hours post-admission, while 617 were not treated. The analysis showed a statistically significant increased risk of progressing to severe forms in the group receiving treatment.



We carried out a study in Bolivia about the consumption of ATB between April and June 2017, to evaluate the community access to the consumption of unprescribed ATB. In 70% of the cases people got the AM, 68% of them by direct recommendation of the pharmacist or an assistant salesperson. The fake shoppers were medical students who simulated either respiratory infections or acute diarrhea. The scenario is not different now in the COVID-19 era. In the city of Santa Cruz de la Sierra, people received signed prescriptions to access treatment schemes without seeing a doctor. Those prescriptions included for example the use of ivermectin which is a drug not yet proved useful for the treatment in the initial phase of COVID-19.



In Bolivia, the sales of azithromycin, hydroxychloroquine and levofloxacin increased by 200%, 130% and 80%, respectively from 2019 to 2020. This Is relevant in Bolivia, where Salmonella resistant to azithromycin was 10% before the pandemics, this percentage must for sure have increased.

In a report by Foster et al., published in Pediatrics in 2019 about patient satisfaction and ATB prescription for respiratory infections using telemedicine, with over 12,800 pediatric patients, the authors reported that 55% of the patients received ATB, of which azithromycin accounted for 12%. Patients who were prescribed ATB were found to be much more satisfied with the consultation than those who did not, and from the physician's side, it was observed that those video-consultations where ATB were prescribed were shorter than average.

There are five important points that we understand as the challenges to implement or adapt an AM stewardship program in the pandemic: 1) the pandemic generated an additional demand for human resources and materials; 2) this need demands an efficient management based on the best available evidence; 3) ASP may adapt their resources and strategies for the management of COVID-19 patients through early detection, developing and updating diagnosis guidelines and protocols and optimizing therapeutic resources; 4) the challenge of carrying out all of this while health care personnel was almost totally assigned to COVID-19 reducing the time spent on other activities; and 5) these new capacities, such as management crisis and mobile applications will represent an opportunity to be used in the future. Another important aspect that we saw is that, at least in Latin America, the ASP team test has been assigned to the front line and this has strengthened the relationship among the team members, and this will probably be beneficial in the future.

This slide shows the results of a recently published study by Stevens et al. about involving ASP in the COVID-19 response.

Involving antimicrobial stewardship programs in COVID-19 response efforts: All hands on deck

Michael P. Stevens MD, MPH, Payal K. Patel MD, MPH and Priya Nori MD

ICHE 2020; https://doi.org/10.1017/ice.2020.69

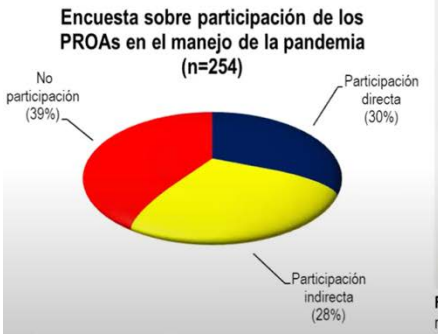


Figura 1. Encuesta vía Twitter en la que se preguntó si los equipos PROA habían participado en la preparación y/o respuesta al brote de COVID-19

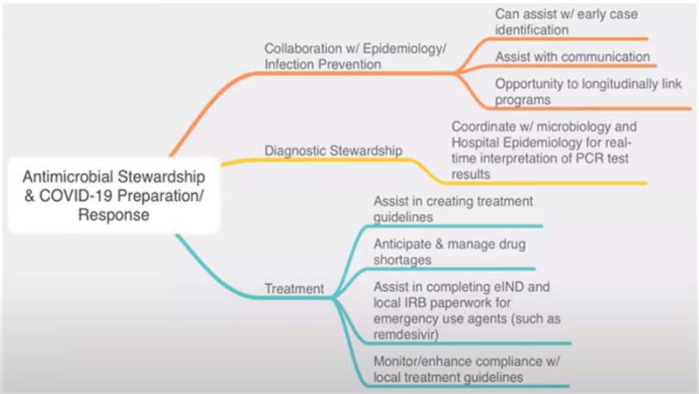


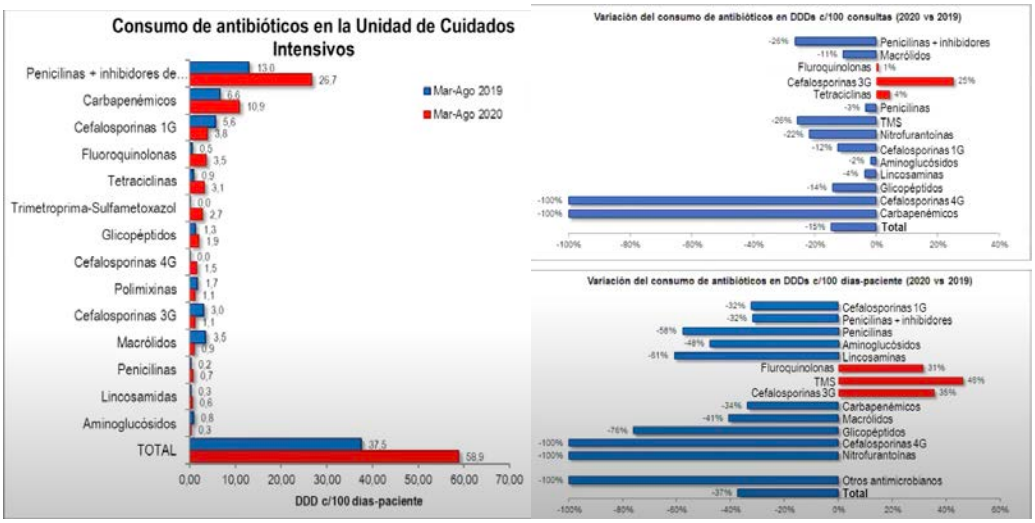
Figura 2. Oportunidades de adaptación de los PROAs para cooperar con la preparación y planificación de las respuestas para el manejo de pacientes COVID-19

Almost 70% of those who answered this survey via Twitter, said that they did not participate or had an indirect participation in the management of the pandemic. However, preparation and response of ASP was a real possibility, by collaborating with epidemiology and infection control, especially in their ability in the use of PPE, the control measures for patients in ICU, improving diagnostic techniques for both

patients with COVID-19 as bacterial co-infections and everything that has to do with treatment based on evidence, periodic evaluation of that evidence and participation in the protocol evaluation committees for the approval of new research protocols, as well as monitoring guidelines compliance.

All of this is mostly what we did in Clinica Foianini, Santa Cruz de la Sierra, Bolivia. The first thing we did was to organize a committee of crisis including the representatives of the different areas. We developed, implemented, and disseminated a set of guidelines for patient management which was periodically updated. We also organized WhatsApp groups which were a useful tool to integrate the emergency team and the ICU team, we also held virtual meetings, and developed mobile applications and a virtual platform (COVID-net) to record the data on the COVID patients in the institution. Another key component was a very intensive approach to rise community awareness to avoid self-medication and the relevance of scientific evidence.

This slide summarizes shows the significant increase in the consumption of ATB comparing the period March to August 2019 vs 2020 in the ICU, while we also registered an overall 15% reduction, due to the lock-down and but also thanks to the primary care physicians who did not increase ATB prescription.



The COVID-19 pandemic represented an unprecedented challenge for the health care system due to the high demand of health resources, which made it difficult to continue some of the routine processes. However, it is possible and recommended that all ASP teams adapt to the new normal. The experiences

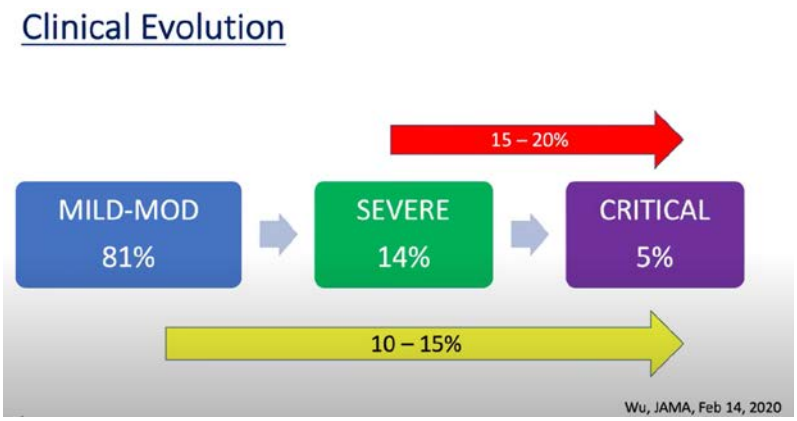
lived and the new strategies of communication should be used in the future as part of the activities of the ASP.

Use of AM in critical care units.

Marcio Borges, Pan American Iberian Federation of Societies of Critical Medicine and Intensive Care (FEPIMCTI)

The Pan American Federation includes 26 scientific societies from America, Portugal, and Spain. I will present our data on the use of AM in the ICUs during the pandemic.

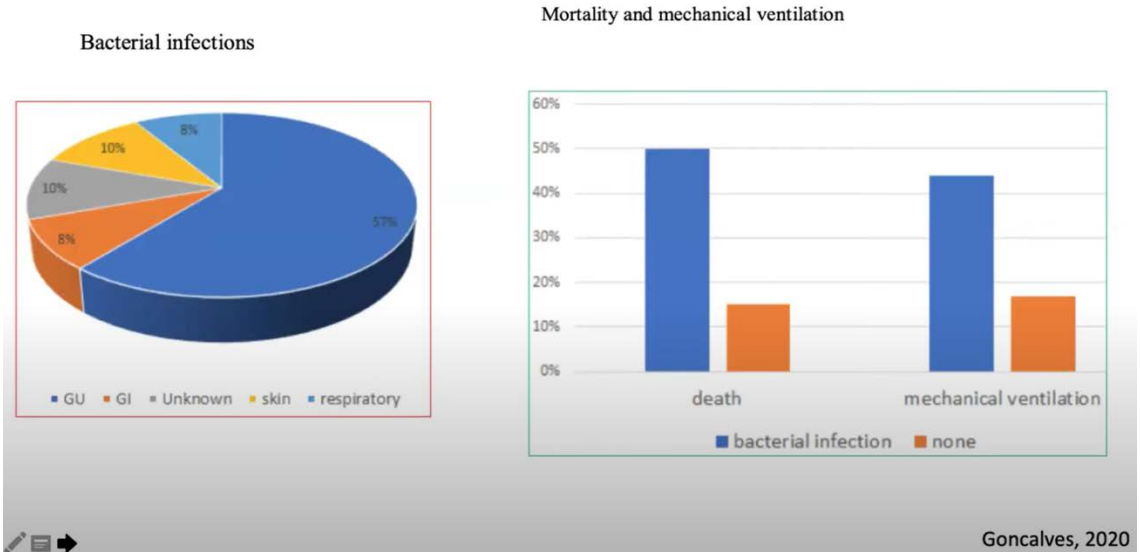
We can estimate that about 5% of hospitalized COVID patients be critical and fall in severity and mortality criteria.



In a meta-analysis published in Anaesthesia, Armestrong et al. found an in-ICU mortality rate of 41.6% across international studies. There were no significant effects of geographical location but reported ICU mortality fell over time.

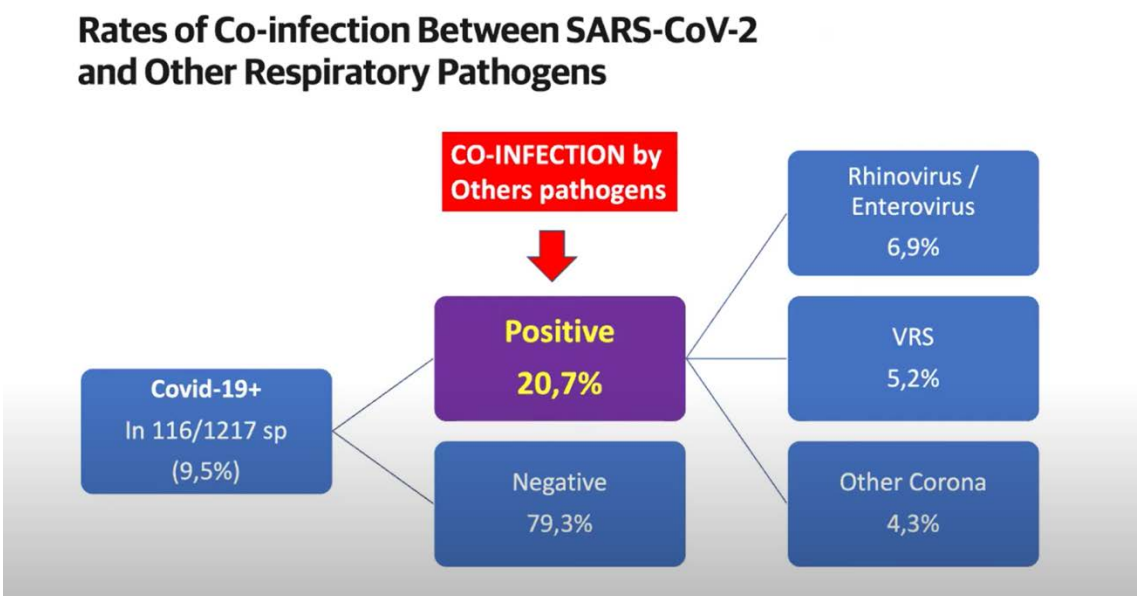
This slide shows the significant impact of bacterial infections on mortality rates and need of mechanical ventilation in patients with COVID-19.

Bacterial Infections and Patterns of Antibiotic Use in Patients with COVID-19



The Spanish Society of Critical Medicine carries out an annual survey (ENVIN-HELICS) on nosocomial infections since 1996, from March to June (4 months). In 2019, the survey included over 28,000 patients of 230 different UCIS from 191 hospitals and showed that 63.57% of the patients received ATB treatment, of which 77% was empiric therapy. We look forward to the results during the pandemic, to compare these figures.

A multi-hospital cohort study by Vaughn et al. in 38 hospitals in Michigan evaluating empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19, showed that early empiric antibacterials were prescribed in 56.6% of the patients, while only 3.5% had a confirmed community-onset bacterial co-infection. Other studies also confirm that the prevalence of confirmed community-onset bacterial co-infections was low, as shown in this slide on the study by Kim et al. published in JAMA.



The use of ATB in the COVID era is undoubtedly high. These are the percentages of AM use at hospital admission or at the ICU:

ATB	%
PROPHYLATIC (Preemptive)	0-55%
EMPIRICAL	25-87%
DIRECTED-THERAPY	>93% (¿?)

In the previously mentioned study by Vaughn, where empirical ATB therapy averaged 63,4%, these were the most frequently used ATB:

Main ATBs

Ceftriaxone 38,9% (663/1705)

Vancomycin 13,8% (235/1705)

Doxycycline 10,9% (185/1705)

Cefepime 10,4% (177/1705)

The guidelines for the management of critically ill adults with COVID-19 will soon be published. One recommendation suggests the use of empiric AM over no AM (GRADE weak recommendation/low quality evidence), but states that if the treating team initiates empiric AM, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology and the patient's clinical status. Bacterial documentation is essential to assess co-infection in COVID-19 critically ill. The use of molecular diagnostic tools and the initiation of narrow-spectrum ATB are key elements of COVID-19 AM stewardship guidelines in the critically ill.

Conclusions

AMR is a global and multi-sectorial problem which demands a coordinated response and is currently more relevant than ever. COVID-19 patients in ICU are highly vulnerable to bacterial infections, due to their underlying diseases and risk-factors. In about 50% of the deaths from COVID-19 patients bacterial superinfection is also present; and the use of AM agents is unrelated to the incidence of infections. Hospitalizations have increased dramatically, and all this situation is impacting on healthcare related infections.

AM stewardship has shown to be an effective tool in the fight against AMR. However, these programs still face tremendous challenges in the region, such as the lack of standardized and updated treatment guidelines, lack of continued medical education, limited diagnostic capacity of the laboratories, limited reporting and surveillance of AM use, and lack of financing.

It is particularly important to consider that the inadequate use of ATB is not exclusive of human health care, but also includes veterinary and agricultural sciences. The high empiric use of AM in ICUs during the pandemic demands high monitoring efforts.

ASPs have faced tremendous challenges particularly during the first stages of the pandemic. They basically needed to re-adapt to the new scenario and some developed a new capacity of crisis management that will be an asset to be used in the future.

Medical education and training, program monitoring, increased technic, and economic resources, as well as education for the public, remain the key strategies to revert the inadequate use of AM agents.