Written responses to open questions of the webinar 'Bringing new treatments for drug-resistant infections to all who need them', originally broadcast on 16 June 2020. See webinar recording here: https://revive.gardp.org/gardp-bringing-new-treatments-for-drug-resistant-infections-to-all-who-need-them/

Question asked	Response from the speakers
What targets are being explored to dramatically reduced antibiotic resistance? I ask this especially because all antibiotics discussed target essential proteins/targets of pathogens?	In general, antibiotics target bacteria by interfering with the biosynthesis of cell wall components/membranes, proteins synthesis, or nucleic acids. Antibiotics currently used in patients kill or inhibit bacterial growth by targeting one or more of those macromolecular targets. GARDP's focus is on finding novel chemical matter that inhibits or kill Gram-negative bacteria via interaction with new targets and with a low potential for resistance development. Also, there should be a concerted effort during development to model and understand the doses needed to minimize the potential to select drug-resistant bacteria.
Thanks to GARDP for your excellent work. Can Venatorx remove biofilms - the pathogens' first resistance response? Every pathogen on the WHO list is a biofilm-former. No known antibiotic can remove biofilm at non-toxic doses -- which is why they fail in later stage clinical trials. If you remove the biofilm, even a very low dose of widely available, ineffective antibiotics -- including penicillin -- can kill these AMR pathogens -- offering rapid global access.	Cefepime-taniborbactam via the partner antibiotic, does demonstrate in vitro activity against bacterial species such as *Pseudomonas aeruginosa* and members of the Enterobacterales known to form bacterial biofilms. However, there has been no specific assessment of the combination in treating and disrupting biofilms. As you know, bacterial biofilms are intrinsically resistant to antibiotics and biofilm infections remain a significant challenge to treat. Also, it is important to note that that biofilms play a more important role in chronic vs acute infections. Biofilms are very important when trying to combat infections in orthopaedic implants, or in lung infections in cystic fibrosis patients, but although important, they are less critical in acute infections in hospitalized patients.
How much time does our body take to become resistant to a drug? What dose should not be taken?	It is bacteria that can become resistant to antibiotics and not the human body. Antibiotics are used to treat bacterial infections, and there are different types of antibiotics that are used to treat different infections caused by different bacterial organisms. The dose is established during the testing process and will vary depending on the antibiotic, the patient, and the type of infection.

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What is the situation with carbapenem resistant Gram-positive bacteria? Are they known to be causing HAIs?	Carbapenem-resistance in Gram positive bacteria usually results through mutations in the genes encoding the target penicillin binding proteins. There is less selective pressure for this mechanism of resistance compared to the varied mechanisms of resistance in Gram-negative bacteria. Also there are alternative treatment options for carbapenem-resistant Gram-positive bacteria (including glycopeptides, oxazolidinones, lipopeptides). Methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) remain the Gram positive pathogens of greatest concern.
Can you provide a link to the "High Priority" bugs list?	https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf
Is meropenem approved for neonates as young as 3 days old?	It is approved for use in neonates as young as 3 days old. Here is a link to the US dosing recommendations for meropenem. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050706s037lbl.pdf
Does Early Onset Sepsis and Late Onset Sepsis decide the course and drug of treatment?	It depends on the setting, but yes it can. Below is a link to a review that was done for WHO on the different guidelines for diagnosing and treating neonatal sepsis. As you can see some guidelines differentiate between early and late onset sepsis, but not all. https://www.who.int/selection_medicines/committees/expert/21/applications/s6_paed_antibiotics_appendix4_sepsis.pdf
I may have missed this, but what if any interest does GARDP have in novel modalities like phage therapy?	Our clinical development focus is on therapeutic interventions that are ready for evaluation in patients. Also, they must align with our target product profiles and focus on the WHO priority pathogens and priority populations. We do not implicitly state whether we are actively considering novel treatment modalities but for these we will need to see a clearer development pathway with demonstration of proof of concept. Also understanding of how the therapy will develop as a final “drug product” is important to understand the related access and regulatory challenges.

Question asked	Response from the speakers
Does developing an antibiotic for children differ from adults or is it more the regulation involved in approving drugs children is more complex?	Usually antibiotics are developed for use in children and adults unless there are specific reasons where it would not be appropriate due to side effects that could affect a child's development or disease process is not seen in a particular population. Generally, paediatric trials will only start once the phase 3 adult trials have completed and established the adult dose, and the treatment is effective and has an acceptable safety profile. Using the adult data trials are designed to establish the appropriate dose and evaluate safety in a paediatric population. Generally, clinical trials are designed to target the exposure to the drug (i.e. levels of drug) is similar in children and adults. The regulatory agencies generally require 1-2 trials in children of all ages to establish the correct dose of the drug in children of all ages and that this dose is safe for use in children. Examples of Paediatric development programmes for all disease areas including antibiotics can be seen here: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_pip The regulations are no more complex than they are for adults but *conducting* clinical trials in children is more complex than it is in adults. It's important that the trials are designed minimising the impact on the child and their family. This includes but is not limited to: • reducing the number of invasive procedures as much as possible, whilst still meeting the requirements of the study protocol • Using an informed consent / assent process which needs to cover both parental informed consent but also assent from the child (sufficient to their level of understanding Lastly, but by no means least, is that whilst the EMA and the FDA require paediatric data and grant companies' incentives such as financial incentive in the form of additional 6 months marketing exclusivity for completing the paediatric development. Paediatric clinical trials are a challenge to conduct as well as being expensive and the market for new antibiotics is usually limited.

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Does antibiotics prescribed after a clinical diagnosis increase the potential for resistance to develop?	This is difficult to answer in this format but generally yes. Clinical diagnosis requiring antibiotics must be based on a diagnosis indicative of a bacterial infection and with additional evidence to further guide the type of presumptive therapy. Additionally, evidence-based guidelines for certain indications such as sepsis and neonatal sepsis support the early initiation of antibiotics therapy in the absence of positive culture. Emergence of antibiotic resistance can be delayed through appropriate prescribing including avoidance of antibiotic treatment for viral respiratory tract infections; use of narrow-spectrum antibiotics when possible; and use of antibiotics for the shortest duration that is effective for the treatment of a particular clinical syndrome.
For priority pathogens would more specific narrow spectrum antibiotics be more effective as a treatments than broad spectrum antibiotics?	In principle. yes, but the development of narrow spectrum antibiotics to target specific pathogens requires an accompanying diagnostic that will identify the pathogen and any drug-resistance. For neonates in particular this is a challenge as the blood culture positivity rate can be quite low, although this is also dependent on the setting, (community vs district general hospital vs tertiary referral hospital).
Will reducing the frequent use of antibiotics help to reduce the drug resistant infections?	To reduce the rate of drug resistant infections, it is important to address appropriate use rather than frequency of use. Please see the response to the question about the use of antibiotics based on clinical diagnosis for examples of appropriate use.
Could you please talk to what types of structural or policy frameworks can be leveraged in order to achieve reimbursement of these novel therapeutics around the world? Are there parallel policy programmes to strengthen these systems in the priority countries to ensure it is ready to adopt the novel therapeutic sustainably if/when it is approved for use there?	There is not a global reimbursement or access framework or fund for antibiotics. There are countries including the UK and Sweden that are piloting reimbursement models that will support availability in a limited use scenario. There are no such reimbursement developments in the priority countries to date but there is movement in some to align an appropriate use strategy with regulatory approval. GARDP recognises that partnerships are required to address the need to make antibiotics available in priority countries in low volumes underpinned by appropriate use strategies. We are currently developing these partnerships to support access strategies for our portfolio and other priority antibiotics

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1 what about microbiome and antibiotic interactions? especially in children as immunity is forming Role of vaccines 2 role of phages 3 online information and diagnostic difference in bacterial and non bacterial infection 4 role of surveillance data to guide national and regional policies	1) This is an important consideration although there is limited data on the impact of antibiotics on the microbiome in neonates. Here is a link to an open source publication that looks at the impact of antibiotics on the preterm infant gut microbiome https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5154371/ Others are exploring the possibility of maternal vaccines for the main pathogens such as Klebsiella Pneumoniae and MRSA, although this is at a relatively early stage particularly for the Gram-negative pathogens. 3) For newborns, in particular, blood culture remains the gold standard diagnostic for neonatal sepsis, even though the culture positivity rate is generally low. C reactive protein (CRP) is used routinely in many hospital settings as a diagnostic to help differentiate between bacterial and non-bacterial infections. Pro-calcitonin is also used but is less common, particularly in resource constrained settings. Newborns, particularly those that are premature have a poorly functioning immune system, diagnostics such as CRP and pro-calcitonin that rely on measuring immune function are useful but the sensitivity and specificity are less than they are for adults and unless a pathogen can be identified treatment would be empiric. 4) Surveillance data is extremely important to guide and inform national and regional policies, this is generally established in high income settings but surveillance programmes in low- and middle-income settings are much less developed, if they exist at all. WHO have established a Global Antimicrobial Resistance Surveillance System (GLASS) and as part of this have developed protocols that countries can use to establish surveillance systems. https://www.who.int/glass/en/

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How can we develop a molecule that shows effectiveness against one of the critical pathogens?	Firstly, it must be demonstrated that molecule is effective in the "test tube" against the bacteria on the critical list. There are streamlined regulatory pathways in the FDA and EMA to guide the development for antibiotics for these priority pathogens although there does need to be more guidance for the development of non-traditional antibiotics. These pathways outline the studies and evidence required to support a regulatory submission for market approval. Post approval there will be additional data required to support use of the antibiotic for priority populations and to support the appropriate use of the drug for patients with the resistant infection of interest.
For a paediatric new antibiotic drug development how is the clinical trial designed. Will it first be tested in adults and then on the babies	Usually antibiotics are developed for use in children and adults unless there are specific reasons where it would not be appropriate due to side effects that could affect a child's development or disease process is not seen in a particular population. Generally, paediatric trials will only start once the phase 3 adult trials have completed and established the adult dose, and the treatment is effective and has an acceptable safety profile. Using the adult data trials are designed to establish the appropriate dose and evaluate safety in a paediatric population. Generally, clinical trials are designed to target the exposure to the drug (i.e. levels of drug) is similar in children and adults. The regulatory agencies generally require 1-2 trials in children of all ages to establish the correct dose of the drug in children of all ages and that this dose is safe for use in children. Examples of Paediatric development programmes for all disease areas including antibiotics can be seen here: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_pip

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I will appreciate if this gets answered although not relevant to today's presentations. 1.What could be responsible for inhibitory activity observed with extracted supernatant with Isopropanol while there was no activity by the colony or the raw supernatant from the colony 2.How can I differentiate between the inhibitory activity caused by antimicrobial peptides or activity caused by toxins or other artefacts	1. Was the isopropanol removed from the supernatant (I.e by dialysis or freeze drying) before the activity assay? If not, the isopropanol could be the cause of the inhibitory activity. 2. If you want to differentiate you could treat the supernatant with/without proteases. If the activity disappears after protease treatment it would be an indication that the activity is protein/peptide dependent. Alternatively, you could use size exclusion chromatography or a c18 column in liquid chromatography and try to assay for activity the fractions containing peptides.