Written responses to open questions of the webinar 'Inhaled antimicrobials: Do we get the drug to the bug?' by Harm Tiddens, originally broadcast on 28 April 2020. See webinar recording here: https://revive.gardp.org/inhaled-antimicrobials-do-we-get-the-drug-to-the-bug/

Question Asked	Harm's response
For critically ill patients diagnosed with HAP with CRE, is inhaled colistin preferred over IV Colistin, knowing that colistin has poor lung penetration?	In CF we use IV colistin for treatment of exacerbations succesfully even when they were before on maintenance aerosolized colistin. It's a challenge to get aerosol into the lungs. I think for individual patients there might be a role for both aerosol as IV. Check the scarce literature
Thanks for this nice presentation! Do you know if there is a link between this inhaled antibiotics and the development of antibiotic resistance?	Multiple studies in CF have shown that after three cycles of aerosolized AB there is a slight increase in MIC but this does not correlate to clinical response. MIC are of limited value as they are derived from serum levels. In addition there is a huge spectrum of MICs of PMO in the lungs. Hence, at the end MICs are of limited value for aerosolzied AB. The clinical response most important.
What about inhalation of liposomal antibiotics?	We have positive experience with Ambisome in the treatment of chronic Aspergillus. Arikace is an interesting drug for the treatment of NTM.
What about alternating two different antibiotics to address resistance?	In CF with chronic Pseudomonas infection that is what is often done, TOBI/AZLI/TOBi etc.
What is the recomended size of particles to get to the small airways?	Ideal is MMAD between 3-5 um plus slow inhalation. However, this is age and size dependent. Large particles inhaled slowly transport more mass relative to small particles.
For CF patients, in terms of pharmacodynamic properties of antibiotics, do you think concentration above MICs dependent killing antibiotics better than time above MICs dependent killing antibiotics for efficacy?	For Tobramycine it's concentration above MIC. For Aztreonam is time above MIC. However, this concept is a huge simplification as you have a wide spectrum of concentrations depending on severity of structural changes.
If antibiotics are delivered, will they hang around for a long time or be cleared rapidly and how are they cleared?	They are cleared through mucocilliary clearance, absorbed depending on the type of AB, degradated, etc everything is happening.

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Do you think next to Tobramycin there is a need for other aminoglycosides to be developed? If yes what would be the criteria or differentiating factors that the novel aminoglycoside would need to fullfill?	Reduced sptum binding would be my top requirement and improved penetration into biofilms.
What is the highest added value of the inhaled route of administration versus iv for indications such as HAP/VAP? When developing a novel drug should one immediately look into inhaled routes in a Phase II trial or first iv?	Aerosolized route through repurposing is interesting for toxic AB when delievred systemically. However they should not act as an irritant or induce inflammation.
Despite all the problems you describe, inhaled antibiotics are thought to be useful in CF. But so far they don't work in pneumonia. Why the difference?	You need ventilation of the diseased lung. In addition pneumonia reflects a wide range of conditions. Proper patient selection might result in positive results.
Can you speak about the difference in effectiveness between inhaling small molecules and inhaling peptides or other biologics?	That is a interesting field but it would require some additional reading and a little bit of time to answer. I have come across a number of interesting papers.
Is plasma concentrations a good representation of concentrations in lungs if not then what is exact method to measure drug at lungs!	Plasma does not reflect lung concentrations. On a very limited scale BAL studies and using a bronchoscope to positiom small filter paper onto the mucosa have been done. Challenging studies to do. I perfer the CFD modeling.
Fascinating! The "breathing pattern" of ventilated patients in ICU might be somewhat standardized and therefore predictable. Can ventilators be optimized for drug delivery? Bayer conducted a huge trial with inhaled amikacin adjunctive therapy in HAP/VAP patients (on top of iv SOC) but couldn't find any advantage. May the drug delivery have missed the critical segment in the bronchial tree?	I would be intested to learn about the specifics of the delivery device in relation to ventilatory settings. There are people who understand these issues (for example, Jerry Smaldone and Igor Gonda are experts in that field). Heterogeneity of patient population will be another important issue. In general there is poor characterization based on CT images. Without knowing the details of the study you are referring to I would guess that poor expansion of diseased lung areas are the culpit.

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How is deposition (concentration of drug) measured? By imaging?	Computational fluid dynamic modeling (see my references on the slides)
Is it technically difficult to administer phages and do you see problems penetrating the mucosal and other physical barriers?	Basically anything can be delivered in a solution and as long as the delivery device does not damage the phages. I'm not an expert on Phages. I guess the normal epithelial lining fluid will not be a barrier. When there is sputum with free DNA etc it will be more complicated
Do you consider protein binding in the ELF i.e. free drug concentration (instead of total drug) in ELF? Thank you	In Bos et al we try to answer this question. Its about free drug.
If I apply your modeling to a patient with viral disease, do you believe one could get an anti-viral drug into the lung in sufficient levels to kill the virus?	Because of COVID we know that it has a special distribution. Hence the drug deposition should match the distribution at different phases of the infection (Early-Later).
What do you think about using both gentamycin inhalation and intravenous in sputum cultures of klebsiella CRE where gentamycin shows sensetivity?	Gentamycin has been used. Tobramycin is better investigated. In case of open airway iv + aerosol might be a good aproach. There is some resorbtion. Hence serum levels need to be monitored.
How do you measure efficacy of inhaled antibiotics?	This depends on the disease. For CF its FEV1 and CFU. Quality of life measurements, time to exacerbation etc are all being used as outcomes.
What percentage of drugs (eg., tobramycin solution) enters the bloodstream?	It is claimed around 10%. However this absorbtion is variable depending on the disease condition. Using nebulized tobramycin we do not monitor for through levels. When combining with iv, PK becomes unpredictable hence in general we do not combine tobramycin iv with nebulized tobramycin.
What is your opinion of using inhalation as route to deliver antibiotics to other parts of the body, not just to lungs?	It is being used. I have not keep track of the literature. But is has been used for Morphine. Insuline has been tried but efficiency was not high enough. Important is that the inhaled drug should not induce airway toxicity. The inhaled route is interesting for vaccination!

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Thanks for your presentation, this was great! Have you done any studies looking at how excipient impacts drug deposition in the lung, particularly glycerol? Does it have any impact beyond influencing particle size?	For fluids any excipient will impact upon the physicochemical properties of the solution and thus upon the aerosol characteristics. For specific questions I refer to my friend Erik Frijlink he is a pharmacist with great expertise (h.w.frijlink@rug.nl).
If bacteria are present in multiple areas of the lungs, would it make sense to formulate polydispersed dry powders that could deposit in different lung regions, instead of monodisperse powders that would target a particular lung area?	The challenge is the small airways. There will be always a concentraion gradient. High central, lower peripheral. Hence monodisperse has been used to more efficiently target the small airways.
Regarding the AZLI modeling, the treatment for the airways seemed clear, but how were the parenchymal concentrations estimated (color coding of lobes), since the fluid dynamic model did not seem to extend to the alveoli?	Beyond the visible airways we extended airway dimensions using the Phalen model. We just computed airway concentrations. Not parenchymal. See Bos et al for details.
Does fluid flow in the lungs assist in the distribution of drugs?	In case you main blood flow to compartments. I guess it does. The vascular bed in the mucosa is as dense as in the heart. Any fluid congestion will impact upon the airway dimensions. To what extend this will impact upon deposition patterns I could not tell you.
Size and surface area of particle has much to do also for inhaled delivery. Can u please comment further on this? Thanks	The way aerosols are tested size and shape are included. MMAD is the behaviour of a particle comapred to that of a water particle of a given size. Porous particles can be relatively big but they behave like small water particles.
With all variables discussed how does this effect clincial trial design of new inhaled antimicrobials ?	I guess that will be different for the different programs. Computational fluid dynamic modeling is more and more integrated in preclinical development. However most people I come across are not aware that aerosol therapy is not resulting automatically in high concentrations within the airway.

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What are the time periods that these aerosolised antibiotics are used i.e are they used as suppressive therapy or treatment or both depending on the patient?	For CF it is used in a one month on one month off regimen. The gap months are filled up with another inhaled or oral antibiotic when needed. It is felt that this 'gold standard' is historically grown and not necessarily the most optimal regimen.
Roughly how large is the difference in concentrations achieved in the small airway using optimal and suboptimal TIP inhalation technique? One of your slides appeared to show a less than 50% difference. Is this roughly accurate?	This is roughly correct. Perhaps even more important is the huge range within each scenario. For details: Effect of Inspiratory Maneuvers on Lung Deposition of Tobramycin Inhalation Powder: A Modeling Study. Meerburg JJ, Andrinopoulou ER, Bos AC, Shin H, van Straten M, Hamed K, Mastoridis P, Tiddens HAWM. J Aerosol Med Pulm Drug Deliv. 2020 Apr;33(2):61-72. doi: 10.1089/jamp.2019.1529. Epub 2020 Feb 19.
Is efficacy due to delivery to the site of infection or absorption into the blood and systemic delivery?	For many drugs absorbtion is limited. Lung dose is in general far too low to obtain significant systemic concentrations. The absorbed dose could theoretically contribute to treat the poorly ventilated areas through the bronchial arteries.
How do the physicochemical properties affect the ability to get to the site of action?	Very important for nebulized solutions as it will detemine particle size distribution. For dry powder formulations hydroscopic growth might affect particle size and thus depposition pattern.
A very general question: while inhaled therapy seems to be potentially useful in a number of airways and lung infections, the clinical experience is that it is only in bronchial infections (typically bacterial inefections in cystic fibrosis patients) that reproducible successes have ben obtained while in alveolar infections or in infections deep in the airways (such as infectiond in a patients with brochiestasis) sucesses have been at best variable and often have been insufficient to gain approval and registration of the proposed medication and apparatus. What has been missed and what would be you suggestions for those wishing to to try again developping uinhaled therapies ... and to get approval ?	For bronchiectasis patient selection will be of key importance (inclusion exclusion criteria). Proper phenotyping including chest CT and centralized image analysis is of key importance to understand the response to inaheld antibiotics in subgroups.

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Now, a micriobology question: while concentrations far above the MIC will eradicate the majority of the original inculum if it wwas in an hogenous medium, what about (i) anheterogeneity in the distribution resulting in some areas being exposed to much lower concentrations where bacteria may remain unaffected; (ii) the exustence of persisters (which are dormant bacteria that will NOT be killed even if exposed at 100 x the MIC but which will regrow as soon as the antibiotic therapy is stopped), and small colony variants (SCVs) the typically are quite resistant to many antibiotics and notorious for being very difficult to elminate partly because they survive intracellularly but which, again, may be released and multiply as soon as the antibiotic is stopped) ? Elimination of persisters and of SCV's is obtained in healthy patients mainly by the immune system. But in a semi-closed area as a lung and in aldter patients (most at risk), these may not operate as it should, which could explain why even inhaled antibiotics fail...	I fully agree. The lung is not a single compartment. Hence there will be a wide range of responses throughout the lung even when there would be a homogeneous population of microorganisms. In reality there will be a very dynamic spectrum of resistant and sensitive micoorganisms. Inhaled antibiotics will alter the spectrum. This understanding is of key improtance to understand treatment succes and (partial) failure.
A bit off-topic: Have CF patients been appreciably impacted to date by COVID-19? If so, have inhaled antibiotics remained helpful in preventing the bacterial aspect of the pulmonary infection?	CF patients are very little affected by COVID with the exception of post transplant patients. Risk awareness has for sure contributed to this. A very well trained immune system might have contributed to it as well.
How will treatment of COVID patients differ?	Evaluating the CTs of COVID CTs. Superinfection will play a role in some patients. Most centers use pragmatically early anibiotic treatment in admitted patients. Aerosolized treatment in COVID-19 adds to the risk of spreading the virus. In addition patients when dyspnoeic might not appreciate inhaled drugs.