

# Non-traditional antibiotics: what will it take to convincingly develop a virulence inhibitor or similar indirect agent?

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22 Apr 2018 – ECCMID (Madrid, Spain)

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Newsletter: <http://amr.solutions>

*I am going to cover a LOT of material today and taking notes will be hard. My slides (& those of my co-presenters) will be available shortly via a newsletter and blog post on my website (see above).*

# Agenda

- Perspective
- Defining scope:
  - The core problem
  - Language to guide conversation
- Discussion of non-traditional products that...
  - Seek to treat infections
  - Seek to prevent infections
- Next steps & Summary

# Perspective

- I am going to sound like a cranky old man who talks too fast
  - Old: I'll ask for leniency on this ... isn't 60 the new 40? More yoga!!
  - Cranky: Yes, but driven by "Tears today vs. tears tomorrow."
  - Talks fast: I am from Texas, but I did not get the slow speech gene!
- In truth, I have always loved the idea of virulence inhibitors (and similar such ideas)
  - But, I have over time come to realize just how hard it will be to develop such products
- This talk is an effort to crystallize my understanding of the tension in these opposing viewpoints
  - Various attributed\*: "A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty."
  - I am seeking pragmatic optimism!

\*See <https://quoteinvestigator.com/2017/07/26/optimist/> for more on the source(s) of this quote.

# Goal for today

- **Take a step** towards defining an approach to talking about developing such products for human use\* via 5 categories (4 for therapeutics, 1 for preventatives)
- **Analysis of ...**
  - What makes each category distinctive
  - The strengths & weaknesses of each category
  - Ways to approach development within each category
- **Acknowledgements:** The best ideas are from debates with those below and all errors are mine!
  - Speakers: Sumati Nambiar, Marco Cavaleri, William Hope
  - Other colleagues: Ursula Theuretzbacher, Kevin Outtersen, Tom Shryock, Jeff Watts, Ed Cox

\*Non-traditional and alternatives are being intensively studied for use in Animal Health. While the science is the same for Human and Animal Health, the development issues are very different. To keep things manageable, I am going to stick almost entirely to Human Health in this talk.

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  - Useful literature, both general and from Animal Health

# The core problem

- All products must showcase their distinctive value
- **This is not a regulatory issue per se.** Rather, this is what we naturally ask of anything
  - Prove to me that it works!
  - How is it better / useful?
  - In what settings can that advantage be seen?
- For antibiotics, limits on the routinely possible studies (next slides) create a substantial hurdle
  - Superiority is (usually) out of reach
  - Non-inferiority studies are relatively unsatisfying
- **Beg for the bad news\***: If you're not clear on this, you are heading into a world of hurt

# Trial Design 101: Two study designs – everything reduces to one of these

- Superiority studies
  - X vs. Y, with an aim to show X beats Y
  - TEST vs. placebo, for example
  - Preferred design – result is unambiguous
  - Everybody likes the idea of Better
- Non-inferiority (NI) studies
  - X vs. Y, with an aim to show  $X \approx Y$
  - Messy, harder to do accurately, confusing
- But, we (almost) always use NI for new antibiotics
  - **Why?**

# The paradox of antibiotics

- We want new drugs for bad bugs
  - The advantage of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection
- But, asking for clinical data leads to a problem
  - Trials must (usually) be designed to avoid superiority
- Example: Limb-threatening infection due to MRSA\*
  - It is not ethical to randomize to methicillin vs. NEW
  - Must instead do something like vancomycin vs. NEW
  - Must NOT enroll if resistant to NewDrug or comparator



# This idea is very, very hard

- Non-life-threatening illness (e.g., migraine)
  - Delayed effective therapy is not dangerous
- Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival
- **Infections: We routinely produce Cure of potentially fatal illness**
  - And, it's hard to improve on Cured
- But, the idea of non-inferiority is confusing
  - “We want a *better* drug.”
  - I get it, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) becomes inadequate
- Next 2 slides: Let's discuss in two other ways

# In Infection, superiority means something bad has happened: Plazomicin and CRE<sup>1</sup>

- In 2012-13, colistin was the only alternative for CRE. A study of plazomicin vs. colistin-based SOC<sup>2</sup> for CRE was plausible
- Plazomicin wins, but efforts to control CRE made it very hard to find cases & enroll (note small N). Cost was \$1m/case!
- And, 40% mortality is not good!
- **Future studies will need to use plazomicin (or one of the other new agents with comparable data) as the comparator**

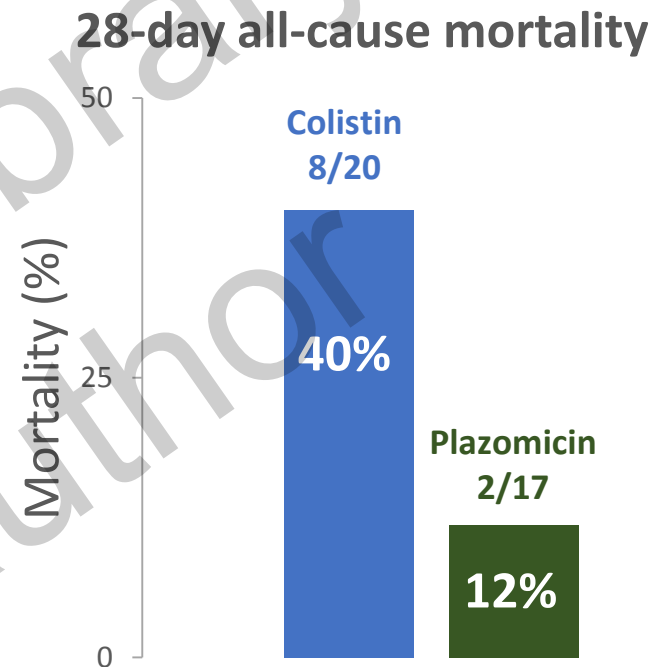


Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from <http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf>

1. CRE = Carbapenem-resistant Enterobacteriaceae

2. SOC = Standard of Care

# But, superiority trials are used in other areas! Tell me again: *Why not in Infection?*

	Migraine	Cancer	Infection	Animal Health
1. Durable cure is routine	No	No	Yes	Yes
2. Placebo is routinely acceptable	Yes	No	No	Yes
3. Existing agents lose utility over time → new agents always needed	No	No	Yes	Maybe
4. New agents are really for use...	Today	Today	Tomorrow <sup>1</sup>	Today

**Points 1 & 2:** Superiority is routinely used in some areas not but others

- *Migraine (non-life-threatening example):* Placebo with rescue is possible
- *Cancer:* Durable cure without complications is not routine and hence continual improvement (e.g., improve 5- or 10-year survival) is always possible
- *Animal Health:* Placebo is acceptable
- *Human Infection:* Placebo not usually acceptable & it's hard to improve on Cured!

**Points 3 & 4:** We need to develop new anti-infectives despite this limitation

- There are negative Public Health issues if superiority is (or becomes) possible!

1.This points to part of the reason why new antibiotics suffer from several forms of market failure. For more on this, see the DRIVE-AB report, various blogs on my website, and any of the writings of Kevin Outterson (his 11 Apr 2018 op-ed in *STAT News* is a great place to start: <https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/>).

2.See this cite for more on Animal Health issues: Page SW, Gautier P. Use of antimicrobial agents in livestock. *Rev Sci Tech* 31:145-88, 2012.

# Solution: The (emerging) 2-study path for new traditional antibiotics

- 1x NI RCT\* vs. a good comparator
  - UDR (Usual Drug Resistance) setting: **both agents are predicted to be active**
  - Done in one of the major indications (cUTI, cIAI, etc.)
- 1x salvage study for highly Resistant pathogens
  - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N too small for this
- Example: Plazomicin initial registration program
  - NI RCT: 1x cUTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin (prior slide)

\*NI RCT: Non-Inferiority design Randomized Controlled Trial. See extended discussion of these trials in Rex JH et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65: 141-146, 2017.

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# What is a non-traditional?

- I am going to differ from prior papers
  - *Mechanism or chemical structure is not helpful*
  - *What matters is what it does or does not do*
- Fleming\* antibiotic:
  - Qualitatively, is like penicillin
  - SSSS: Has the spectrum for a defined syndrome and the speed required to be suitable as standalone therapy
- Non-Fleming = non-traditional = everything else
  - Phage, antibodies, small molecules, large molecules, microbiome ... it doesn't matter

\*Sir Alexander Fleming (6 Aug 1881 – 11 Mar 1955) was a Scottish physician, microbiologist, & pharmacologist. His best-known discoveries are the enzyme lysozyme (1923) and benzylpenicillin (Penicillin G, 1928).

# Other language to note and then (mostly) bypass in this talk

- Alternatives to antibiotics
  - A very broadly used term, sometimes taken to be the same as non-traditional and sometimes taken as a superset that includes non-medicinal tools (e.g., a super smooth catheter to which nothing sticks)
  - I mostly just treat as equivalent to non-traditional
- Potentiator or Enhancer
  - These terms are applied to many different types of combinations. I find them too ambiguous to be helpful.
  - Because of that, I tend to avoid this language. We'll below try some alternative language

# Back to the mainstream...

- For a therapeutic, SSSS opens doors
  - **Spectrum for a syndrome, speed of a standalone**
  - If SSSS, there is at least one setting where you can enroll empirically into a standard NI RCT of NEW vs. a standard comparator
  - This is a predictable path to registration
  - There is some flex on spectrum (see later)
- For prevention, SxxS is the minimum bar
  - **Spectrum must cover target pathogen(s)**
  - **Standalone seems required on a practical basis**
  - But, and as discussed below, prevention has other issues



# The (lesser) problem of the MIC\*

- We are very used to doing an MIC to predict utility of a given agent for a given bug
- But, some categories of products (e.g., true virulence inhibitors) lack an easy path to a test that resembles an MIC
- I think this is a problem we can manage
  - We don't require it for other drug classes
- But, it may mean loss of PK-PD as a strong support for the data used to achieve registration
  - Unless we can find a way to replace the support provided by PK-PD for predicting efficacy of the dose/exposure, we may need to prove utility by doing at least two RCTs rather than one (yuck!)

# What about other potential benefits of non-traditional products?

- Some features of non-traditional products have a very attractive intuitive feel
  - “It’s narrow → less pressure on other bacteria.”
  - “It works via the host and hence resistance can’t arise.”
  - “It will have fewer side-effects.”
- Perhaps true but very hard to prove in a clinical trial
  - **Less development of R:** Carriage of resistant bacteria is imperceptible, but trial endpoints must be grounded in how a patient feels, functions, or survives
  - **Safer:** AE rates are pretty low with most modern agents – it’s hard to show convincing superiority on safety

# Will diagnostics fix any of this?

- Unfortunately, diagnostics do not (yet) have the speed & efficacy of a Star Trek tricorder
- Issue #1: Diagnostics do not create cases
  - If rare bacterium X is present in 1% of cases...
  - ... you still have to screen 100 to find that one
- Issue #2: Time is ticking, referral is not a path
  - In cancer and rare diseases, we don't dawdle but there is time to both make a diagnosis and refer as needed
  - With Infection, minutes count. The patient must present at site that is already running the study
  - This magnifies the problem of finding those rare cases
- These limits noted, we'll look for possible uses

# Finally, know also that I'm skipping product-specific issues

- Examples

- Immune response to product: Lysins (and anything else that is effectively a large protein) might face this
- Delivery of product: Antisense products may require special delivery tools
- Need for product customized to an individual patient: Phage cocktails might need to be customized
- I view all of these as secondary – if a product were compelling, we'd solve these sorts of issues

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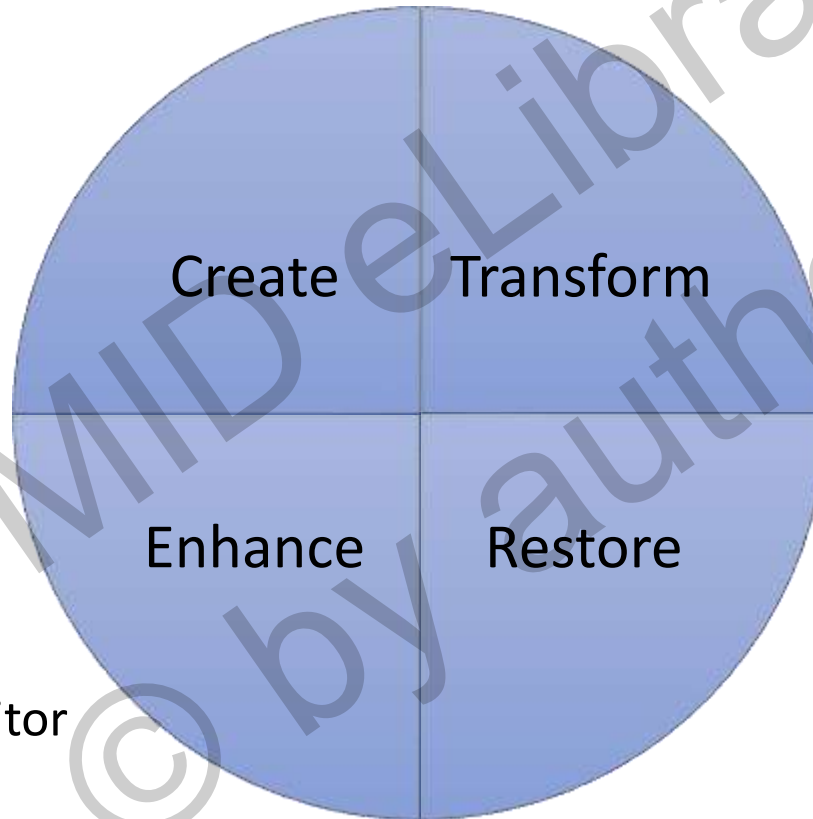
# Treatment: Four archetypes

## Examples

- Phage
- Lysins
- Antisense

## Example\*

- Virulence factor inhibitor + approved antibiotic



## Example\*

- Gram-negative activity from colistin + approved Gram-positive antibiotic

## Example\*

- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

\*The terms "Potentiator" or "Enhancer" have been used for products in all 3 of these categories

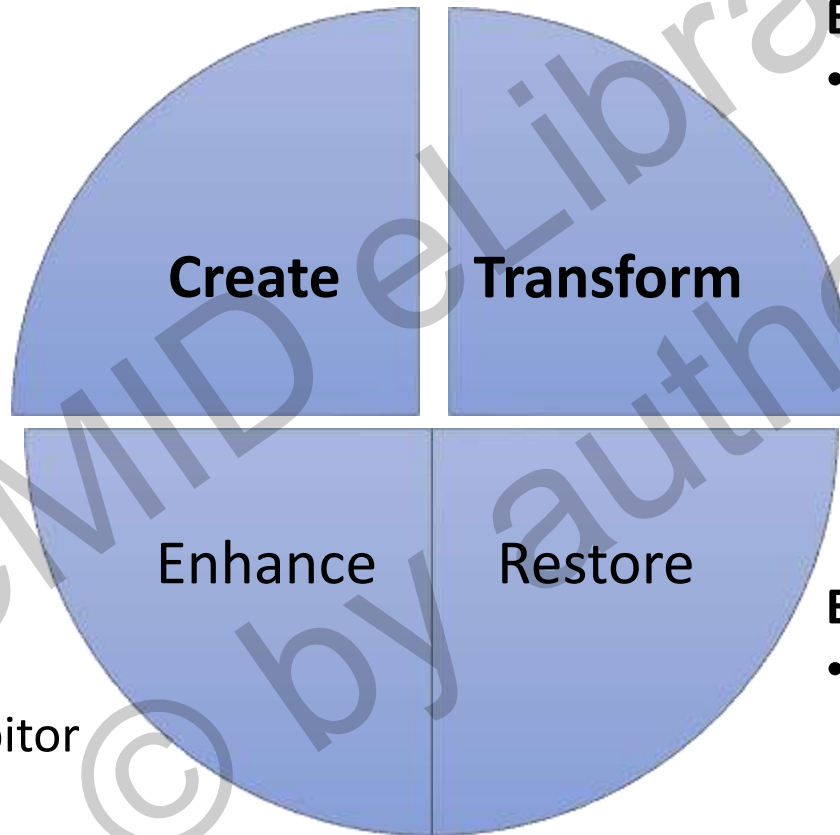
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# Create, Transform: New direct activity

- xxSx: Spectrum, syndrome, speed, sandalone
- Examples:
  - **Create (a new mechanism):\*** Phage, lysins, antisense
  - **Transform:** NEW added to 2nd agent not otherwise active on the target (e.g., polymyxin + known Gram-positive agent where combo has Gram-negative activity)
- In either case, an entity complete in itself
  - Even if it has more than one component
  - Usually has an MIC
- Advantages: Standard NI designs may be suitable
- Hurdles: If narrow-spectrum or not standalone...

\*This would also describe ANY new mechanism standalone molecule, small or large, that is SSSS.



# Narrow-spectrum problem (1 of 2)

- Narrow-spectrum antibiotics require a setting where activity for a specific pathogen can be seen in isolation. There are 4 possible patterns:
- Pattern A: Organism = Syndrome (*N. gonorrhoeae*)
  - Straightforward study design
- Pattern B: Organism appears within a syndrome **and** symmetrical gaps in the spectrum of existing agents make it possible to show activity of NEW:
  - Example: ertapenem does not cover *P. aeruginosa*. So, NEW + ertapenem vs. imipenem shows activity of NEW.
  - Low rate of *P. aeruginosa* is the remaining problem
  - A diagnostic could support selective enrollment

# Narrow-spectrum problem (2 of 2)

- Pattern C: Organism is one of several causes of a syndrome and existing agents often cover organism
  - Ex: *Klebsiella* as a component of cIAI & pneumonia
- This pattern further subdivides into...
  - Normal commensal vs. Always a pathogen
- C1: Commensal pathogen, e.g. *E. coli*
  - The signature of the bug is present in everybody
  - Must find a setting that favors actual infection
  - Possible example: *E. coli* in uUTI might be possible to diagnose with a non-Star Trek diagnostic
- C2: Always a pathogen, e.g., *Salmonella*
  - This might be a sweet spot for a rapid diagnostic

# Standalone problem

- For one of several possible reasons (e.g., lack of speed or limited potency), NEW alone is not deemed sufficiently active to be monotherapy
  - Equipoise cannot be achieved for NEW vs. OLD design
- Instead, NEW + OLD must be compared with OLD
- In this case, NEW + OLD must show superiority to OLD based on a clinical endpoint grounded in how a patient feels, functions, or survives
- This problem also seen with the Enhance category and will be discussed further when we get to that

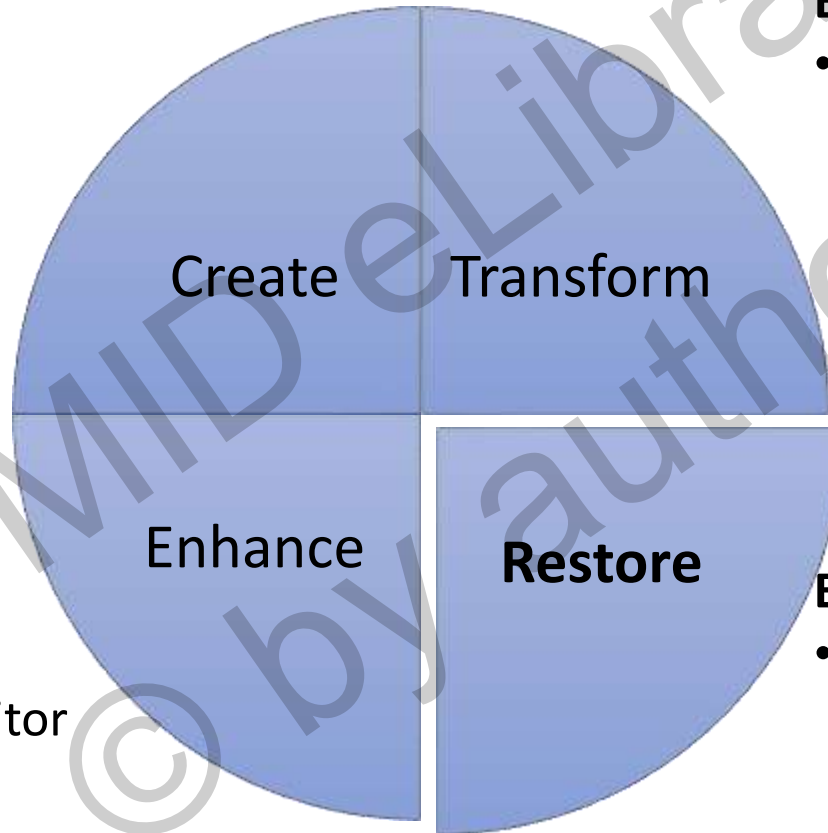
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# Restore an existing agent

- Example: Beta-lactamase inhibitor (BLI) that restores activity of a beta-lactam (BL)
  - BL has worked in past, but R mechanisms now block it
  - With BLI, MIC of BL moves from >128 back to 0.5 mg/L
- Advantages: There is a clear path to development
  - The prior history of the base product gives great comfort
  - PK-PD-based support for dosing should be possible
  - In short, is often very close to SSSS
- Distinctive hurdles
  - Partners must have matching PK (needed by all combos)
  - Narrow-spectrum problem may occur if bacteria in which activity change can be shown are rare

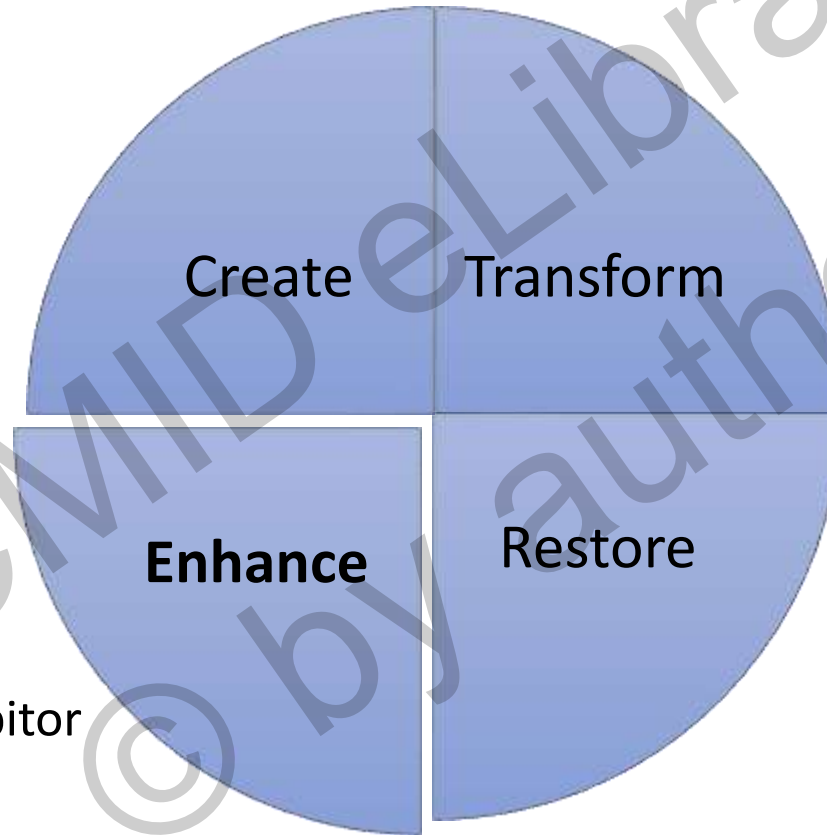
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# Enhance an existing therapy

- Example: Virulence inhibitor or such
  - Usually lacks an MIC equivalent and has no discernible effect on the base therapy in the laboratory
  - Is not thought sufficient alone: Must be used in combination with an active primary agent
- Distinctive hurdles
  - **Base therapy needs to work**
    - Might protect a base therapy from emergence of resistance but doesn't solve existing resistance problems
  - Dose: Lack of an MIC → harder to apply PK-PD
    - If the PK-PD rationale has gaps, it becomes harder to validate dose/exposure logic. You may need two studies
  - Superiority problem: Must show  $NEW + OLD > OLD$
  - May need a novel endpoint to show value (next slide)

# Superiority & Endpoints

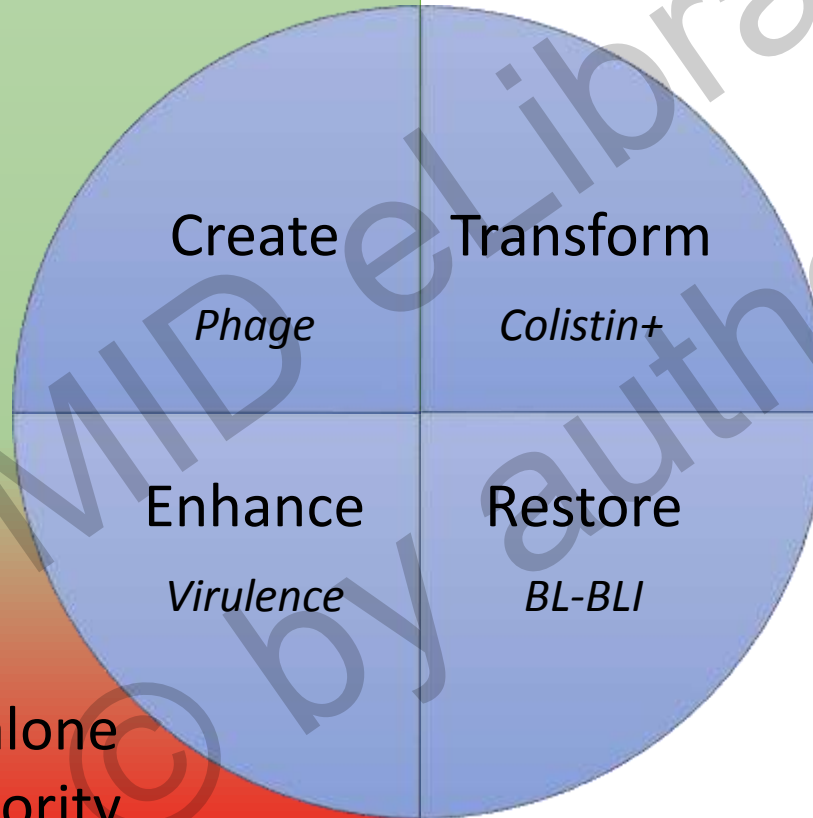
- Ultimately, these agents force a study of this form
  - NEW + SOC vs. SOC
  - And, we will want to see that NEW + SOC is **superior to** SOC
- Are there settings where this might be possible?
  - Endocarditis is my #1 choice: more rapid bloodstream clearance might have a measurable clinical effect
  - But, this is a hard study to enroll and there is so much noise in the data – clinical improvement may be tough
- **Endpoints:** Would different endpoints help?
  - This is fascinating question and worthy of more debate
  - But, whatever is proposed must be compelling. I've not (yet) found ideas outside of “feels, functions, survives” that make sense to me
- **Finally, know that this is not a regulatory problem**
  - The agencies are simply the first to point out the issue
  - Why should I use this? Why should I pay for this?



# Comparing the four archetypes

*Create & Enhance: Novel & difficult*

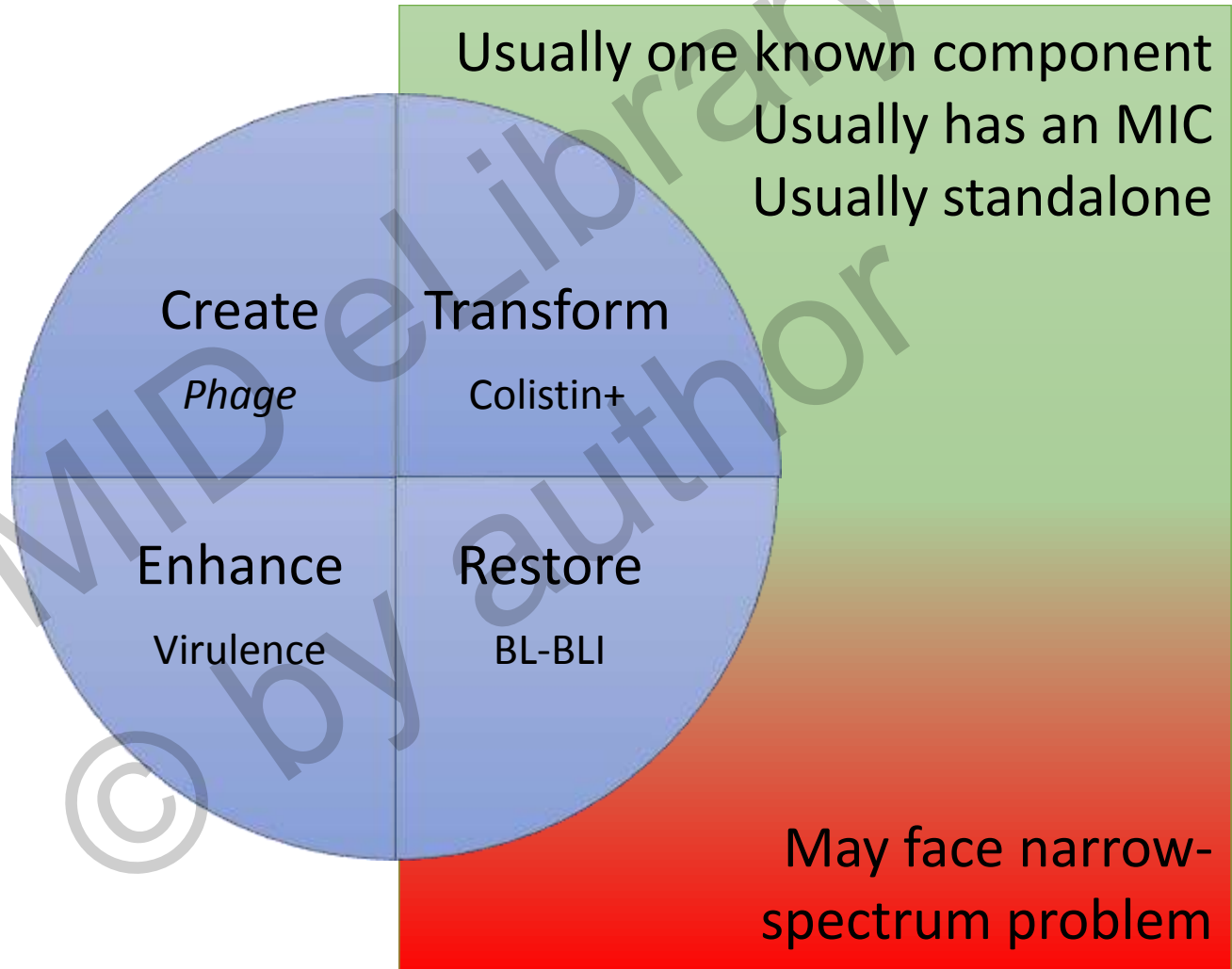
Really different!



Often narrow  
Often not standalone  
May need superiority  
Often lacks MIC (limits PK-PD)

# Comparing the four archetypes

*Transform & Restore: Fewer development issues*



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# Prevention: Surprisingly hard!

- Ex: Antibodies or microbiome products seeking to reduce carriage of specific bacteria
- Key hurdle: **Reducing carriage is not enough**
  - Must show an effect on a subsequent infection
  - Must show this *on top of* best available prevention
  - Frustratingly hard & may require very large studies
- And...
  - Effect & effect size must be interesting
  - NNT (number needed to treat) must be reasonable
  - What replaces the displaced bacteria? Shifting from carriage of VRE\* to *Candida* may not be a good thing!

# Case study: Pfizer's *S. aureus* vaccine (1 of 3)

- 7 Nov 2017: Vaccines and Related Biological Products Committee (VRBPAC) discussed Pfizer's investigational *Staphylococcus aureus* vaccine for pre-surgical prophylaxis in elective orthopedics
- Two core questions:
  - How big does the study have to be if you must show reduction in a serious (non-trivial) clinical infection?
  - In what population can you do this?

# Pfizer's *S. aureus* vaccine (2 of 3)

- P3 trial in population with highest rate of surgical infection (despite good care) they could find:
  - Open, posterior approach, multi-level, instrumented, spinal fusion orthopedic surgery.
  - Read that carefully!!
- Post-op infection rate predicted to be 1.4%
  - Pfizer is running a trial that ([clinicaltrials.gov](https://clinicaltrials.gov)) will enroll over 3 years about 2,600 subjects at 1:1 vaccine:placebo\*
  - Has 88% power to detect  $\geq 70\%$  infection rate reduction
  - This would be a fall from 1.4% to 0.42%
- Question to the Advisory Committee
  - If no safety issues, would data showing efficacy generalize to other orthopedic procedures?

\*Placebo was really best standard of care + placebo

# Pfizer's *S. aureus* vaccine (3 of 3)

- So ... can we generalize to hips, knees, and so forth?
- FDA briefing book comment
  - As “... rates of invasive *S. aureus* disease across other elective orthopedic surgical populations are ... ~0.25% to ~0.5% within 90 days of surgery ...”
  - “... conducting a randomized, placebo-controlled clinical endpoint efficacy trial that includes other elective orthopedic surgical populations would ... (be) ... operationally impractical.”
- My math: required sizes are 10-20,000 **per arm**
- If 0.25% → 0.125%, NNT\* = 800. What's that worth?
  - NNT for influenza vaccine: 10-40 (Kolber MR et al. *CanFamPhys* 60:50, 2014)
  - NNT for HPV vx & cervical cancer? ~300-350 (Brisson M et al. *CMAJ* 177:464-8, 2007)
- All together, no simple answer given efficacy of other tools

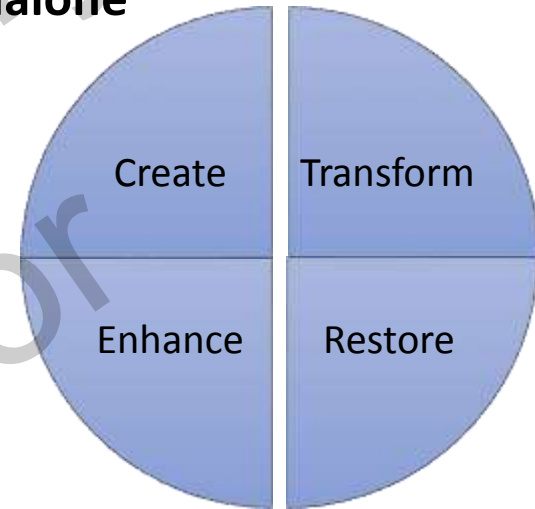
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# Summary

- Fleming: We generally know how to develop these
  - SSSS: Spectrum for a Sndrome, Speed of a Standalone
- Outside this zone: Non-Fleming
  - Create & Enhance: Often VERY hard (superiority likely needed)
  - Restore & Transform: Easier but not easy. Narrow-spectrum issue can be a challenge
  - Prevent: Surprisingly hard (big N needed)
- At heart, the problems are not regulatory ... agencies are simply the first of those who ask hard questions
- *Beg for the bad news: Wishing won't fix this!*
  - We need to find strong solutions to the 4 recurring issues: Narrow-spectrum, Standalone, Superiority, and Endpoints
  - Duke-Margolis workshop on 14 June + other workshops during 2018



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# General literature

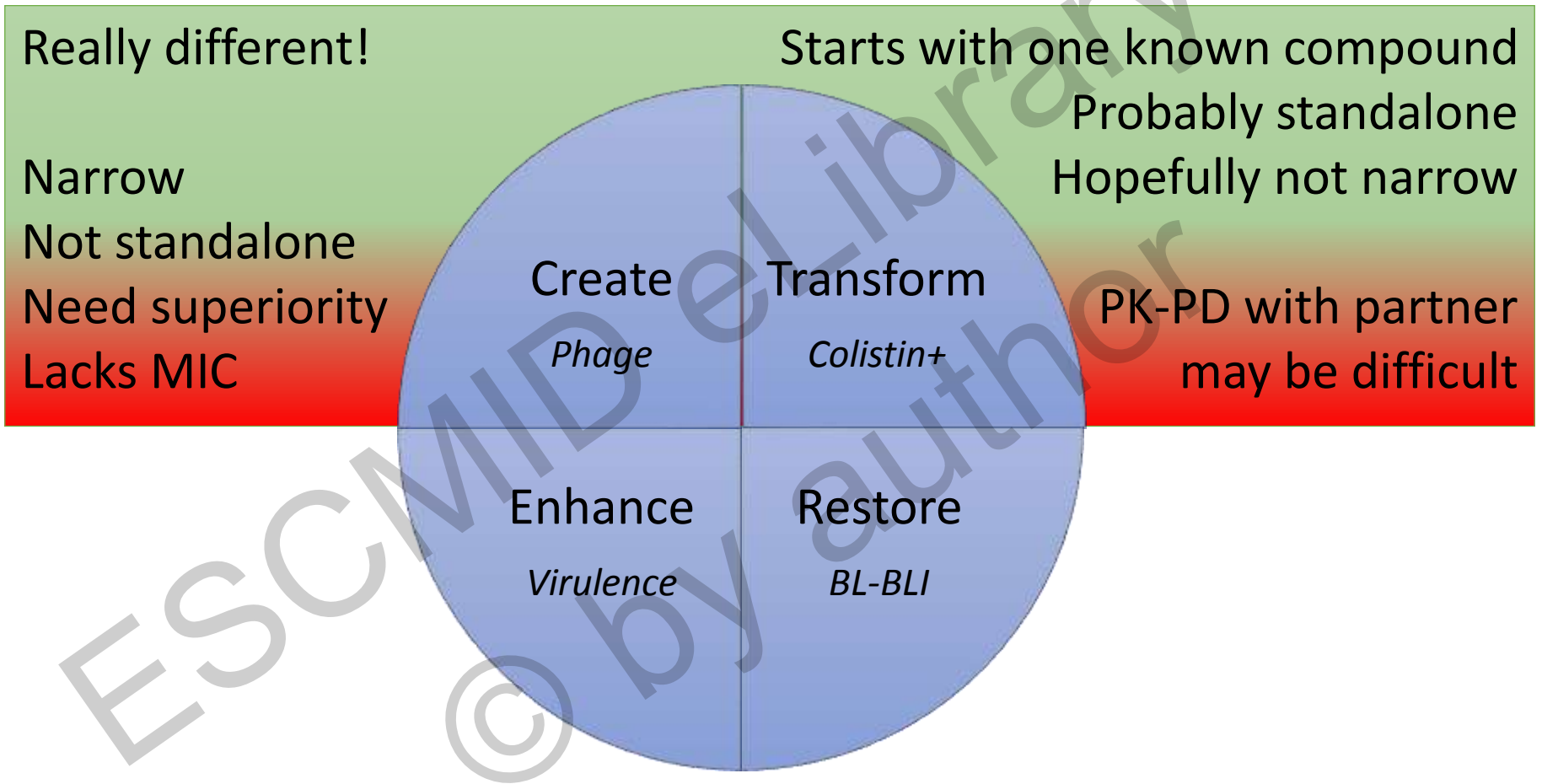
- Czaplewski et al.: Alternatives to antibiotics – a pipeline portfolio review. *Lancet Infect Dis.* 16(2):239-51, 2016.
- Tse et al.: Challenges and Opportunities of Nontraditional Approaches to Treating Bacterial Infections. *Clinical Infectious Diseases.* 65(3):495-500, 2017.
- <http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development>
- Rex et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. *Clinical Infectious Diseases* 65: 141-146, 2017.

# Animal Health Literature

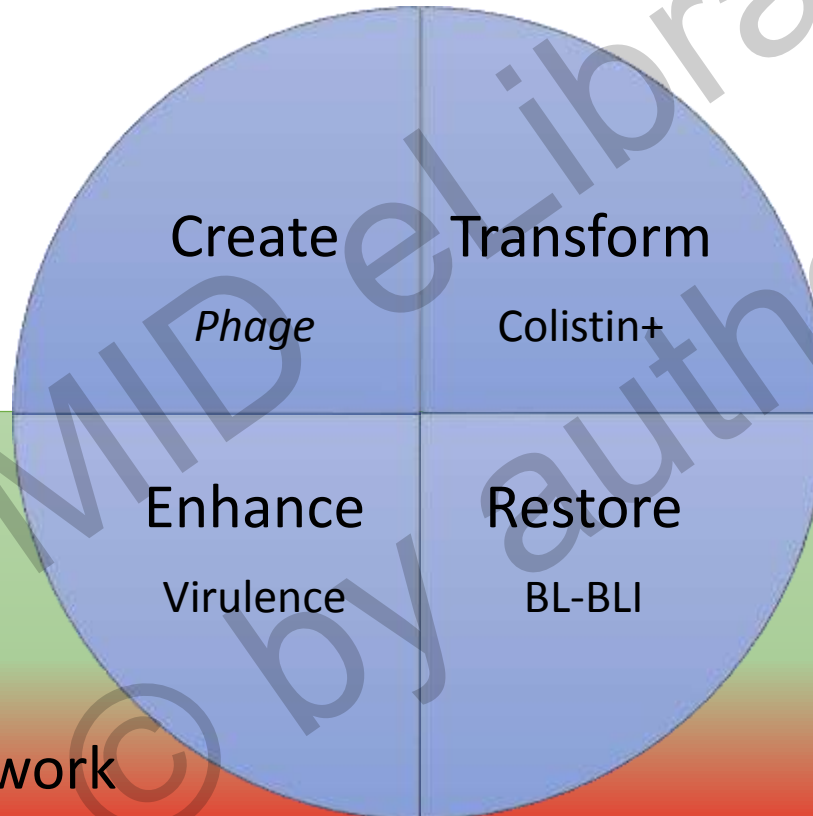
*AH spends a lot of time thinking about these types of tools*

- USDA Alternatives to Antibiotics 2nd meeting held at OIE in Paris 12-15 Dec 2016:
  - <https://www.ars.usda.gov/alternativestoantibiotics/Symposium2016/index.html>
  - See Session 6 where there are 5 excellent talks: EMA, FDA, China Institute for Veterinary Drug Control, and two Industry perspectives
- A 2013 summary (slide deck) by Cyril Gay (USDA)
  - [http://www.oie.int/eng/A\\_AMR2013/Presentations/S8\\_1\\_CyrilGay.pdf](http://www.oie.int/eng/A_AMR2013/Presentations/S8_1_CyrilGay.pdf)
- A 2013 review (manuscript) by Seal BS et al. (USDA)
  - [https://www.ars.usda.gov/alternativestoantibiotics/PDF/reports/AT\\_A%20challenges%20and%20solutions%202013.pdf](https://www.ars.usda.gov/alternativestoantibiotics/PDF/reports/AT_A%20challenges%20and%20solutions%202013.pdf)

# Treatment: Four archetypes



# Treatment: Four archetypes



Really novel!  
One known cpd

Often narrow  
Base cpd must work  
Must show superiority

Usually has MIC  
One known cpd  
Often standalone

May face narrow-spectrum problem

# Thank you!

John H. Rex, MD

Chief Medical Officer, F2G Ltd; Expert-in-Residence, Wellcome Trust; Operating Partner, Advent Life Sciences

22 Apr 2018 – ECCMID (Madrid, Spain)

Email: [john.h.rex@gmail.com](mailto:john.h.rex@gmail.com)

Newsletter: <http://amr.solutions>

*I am going to make my slides available via a newsletter and blog post on my website (see above)*