

Compliance in Antimicrobial Stewardship Programs

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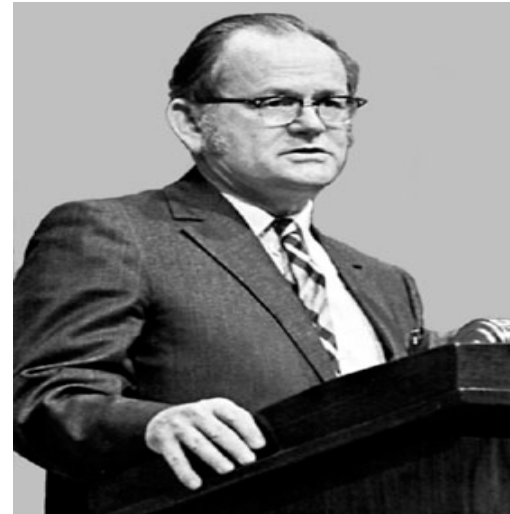
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The Tragedy of the Commons

- *“The ... problem has no technical solution; it requires a fundamental extension in morality”*
 - One sentence abstract
 - Garret Hardin, *Science*, 1968
 - Nearly 50 years later, cited 35,515 times in peer-reviewed literature (as of 01/07/2018)
- The concept of “antimicrobial stewardship”, expressed through ethical practice, is a fundamental extension of the moral imperative to preserve effectiveness for *‘future others’*



www.garretthardinsociety.org

image is of Garrett Hardin, who wrote the now-famous essay in Science magazine (1968) entitled: "The Tragedy of the Commons". Having 'no technical solution' is meant here to imply that while science is important for understanding the extent of the problem (antimicrobial resistance), and for identifying potential technical solutions (informing stewardship programs), effective intervention cannot be put in place without the individual and social behavioral changes that are effected through moral norms resulting in shifts in ethical practice.

...*fundamental extension[s] in morality...*
through codified ethical practices

- *"To preserve the effectiveness [of antibiotics], we simply must use them as judiciously as possible"*
- *"Preserving antimicrobial effectiveness in the future through ethical practices today"*

FDA deputy commissioner (2010)

Global quick-serve restaurant chain (2015)

The quote on the left comes from Joshua Sharfstein, ex-deputy commissioner of the FDA in 2010 whose announcement in this form led to the issuance of Guidance for Industry 209 and 213 and the subsequent removal of growth promotion claims for medically important antimicrobials in the United States. The quote on the right comes from McDonald's Corporation statement of March 2015 announcing their global vision for antimicrobial stewardship.

One set of values

- Human medicine takes precedence over veterinary medicine and animal agriculture
- Precautionary principle should prevail
- Increasing order of defensible use: growth promotion, prophylaxis, control, treatment
- Certain classes of drugs deemed critically important to human medicine should not be used at all in animal agriculture

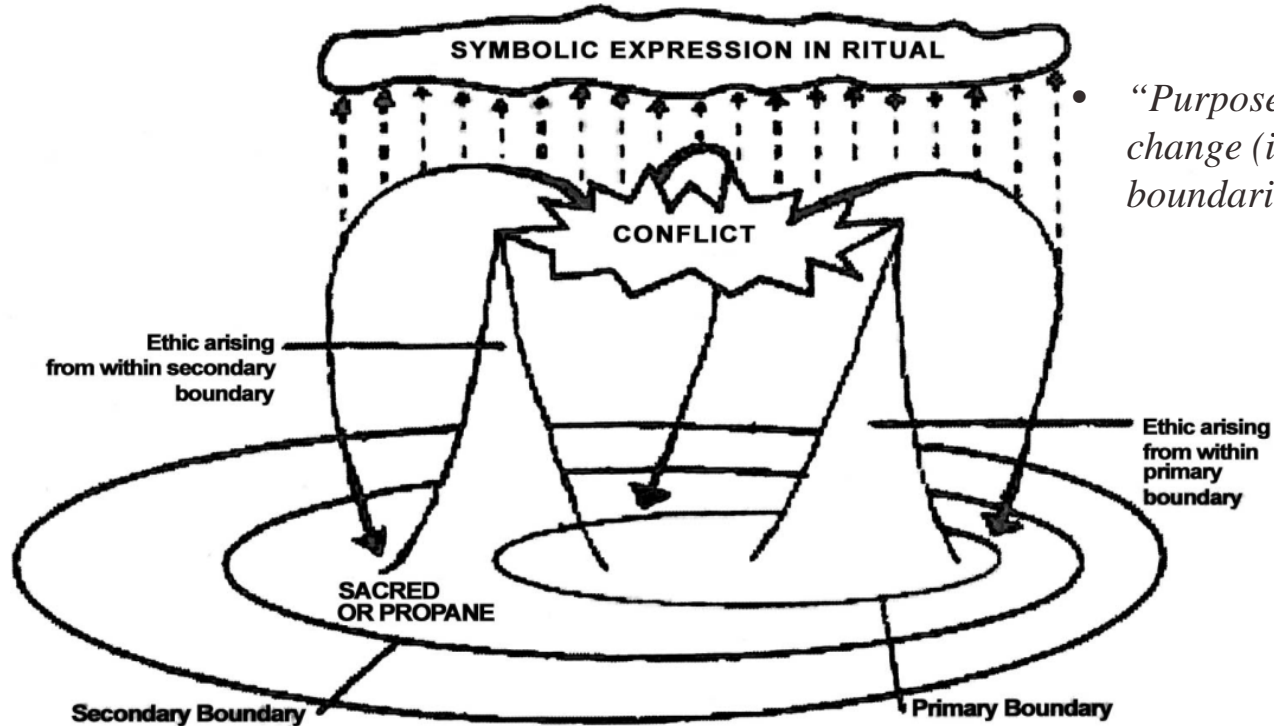
This is a condensed list of commonly stated arguments against the use in animal agriculture of antimicrobials deemed important for human medicine.

Another set of values

- Antimicrobial therapy should be viewed as a last resort
 - A systemic ‘failure’ when animals become ill
- Prevention and control of disease in food animals improves both animal and human health
- Antimicrobials help improve food security in a world with growing needs

This is a second list of opposing arguments for the use of medically important antimicrobials in animal agriculture, including for prevention, control and production purposes.

Systemic intervention – values based



“Purposeful action by an agent to create change (in relation to reflection upon boundaries)” ... (Midgley 2006)

(after Cabrera 2008, and modified by Midgley)

This graphic illustrates the potential for sustained values-based conflict over issues such as appropriate use of antimicrobials. Commonly held values where boundaries overlap and where individuals are not marginalized are the key to sustainable and accepted stewardship programs that meet both animal agriculture and consumer/public health expectations and needs.

Shared values

- Antimicrobials enhance the health and well-being of humans and animals
- There is overuse/misuse of antimicrobials in both human and animal settings
- Protecting the efficacy of antimicrobials for future generations is a good thing to do

These are three examples of values that are likely to be common to both advocacy groups.

Antimicrobial stewardship: production agriculture

- **Target bacterial pathogens**
 - Bovine respiratory disease complex
 - *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida*
- **Non-target bacterial pathogens and commensals**
 - Enteric bacteria
 - *Salmonella*, *E. coli*, *Campylobacter* spp.



The dilemma in establishing stewardship guidelines based on best clinical practices (e.g., susceptibility testing of organisms from clinical cases such as pneumonia) is that for agriculture the primary public concern is of enteric (non-target) pathogens such as Salmonella. Reconciling these sometimes divergent objectives is difficult, but not entirely dissimilar to the challenges of treating pneumonia caused by *Streptococcus pneumoniae* in humans while potentially creating and selecting for resistant nosocomial enteric pathogens in hospitals. The same applies to clinical veterinary medicine for companion animals.

A risk-based framework for agricultural stewardship

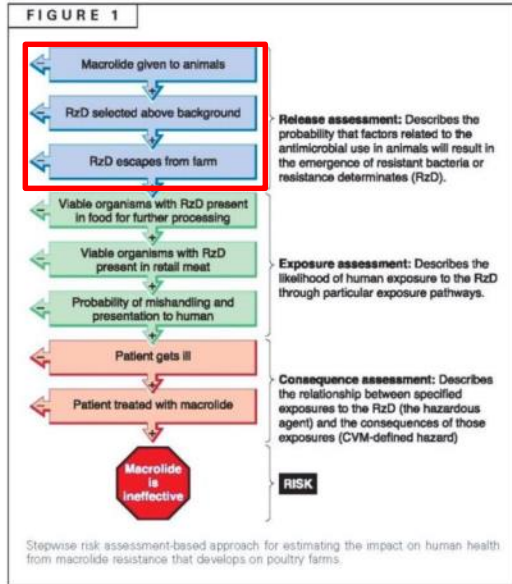
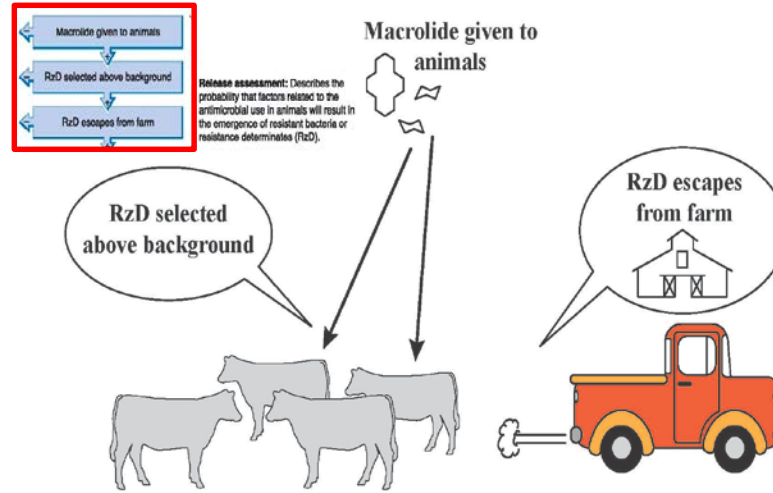


Figure 2: Release assessment schematic: avoiding release of resistance from the farm



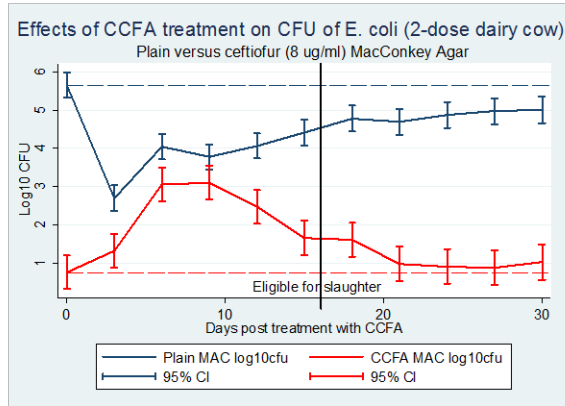
Adapted from Hurd, HS. Microbe 2006

Hurd, H.S., Microbe, 2006

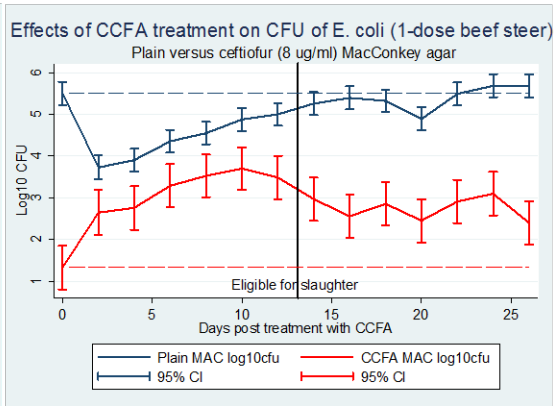
The risk assessment framework put forward by the late Scott Hurd (Iowa State University) in the American Society for Microbiology news magazine *Microbe* in 2006 helps to identify the components that veterinarians and agricultural producers can hope to impact through stewardship initiatives. In this example, limiting the spread of resistance from the farm (escape) means reducing resistant bacteria that expand beyond background levels following treatment and preventing their escape from the farm whether through the food supply or environmental spread through water, air and soil.

Limits of stewardship in agriculture?

Treatment of single dairy cow 2-dose CCFA



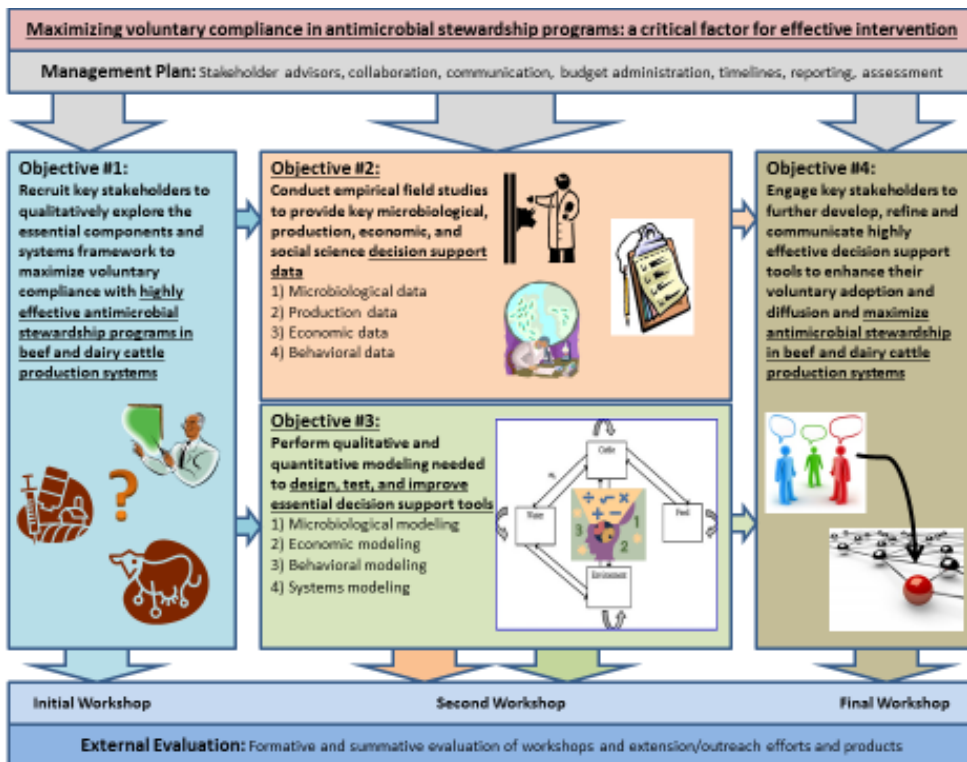
Metaphylaxis pen of steers 1-dose CCFA



Unpublished data courtesy: Norby, Loneragan, Scott, Halbert

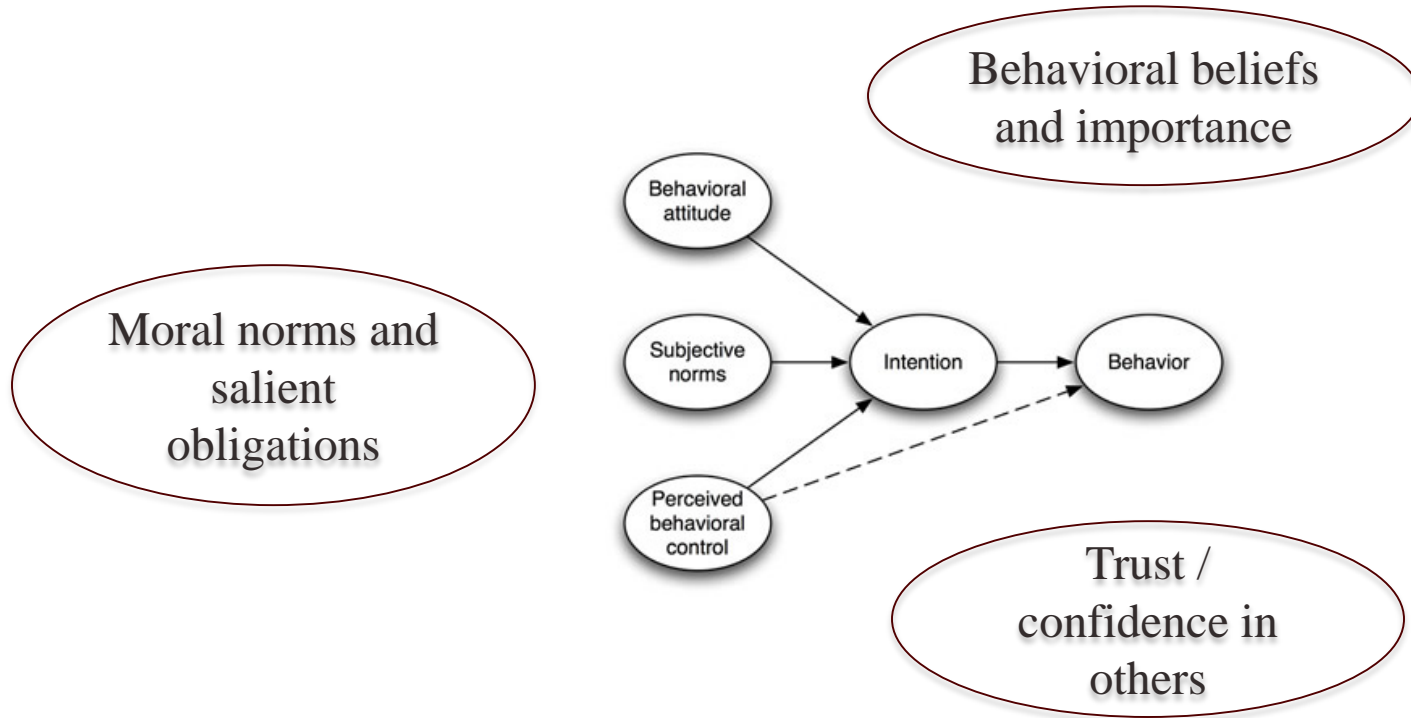
This graphic is meant to represent the very real implications of adopting the Hurd 'release' or 'escape' framework from the previous slide. In this case, the use of a third generation cephalosporin antibiotic (ceftiofur crystalline-free acid – CCFA) in dairy cows (left side) and beef cattle (right side) yield elevated levels of resistant fecal bacteria well past the withdrawal period (vertical line) at days 16 (two-dose dairy cow label) and 13 (single dose fed beef cattle label), respectively. This suggests that stewardship programs that go beyond simply following product labels (i.e., indication, dose, duration, route of administration, slaughter and milk withholding times) will need to be dynamic and responsive to measured changes in the bacterial populations over time.

An ongoing stewardship project



This figure is a schematic illustrating an ongoing USDA-NIFA funded integrated project that seeks to engage stakeholders in cattle production and public health/consumer advocacy to better define stewardship and to inform decisions that go beyond product label requirements using empirical data and mathematical models.

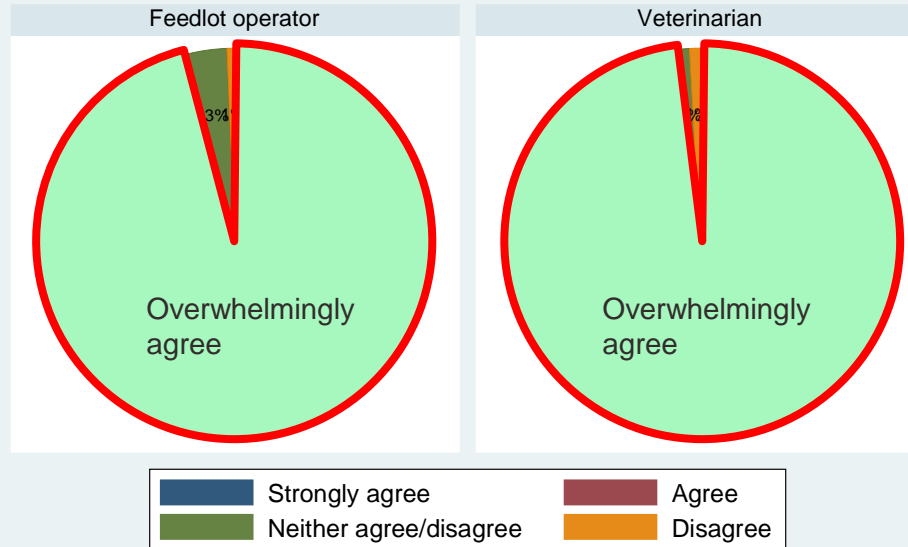
Theory of Planned Behavior (Ajzen 1991): adapted for production agriculture



The central figure is the core of the Theory of Planned Behavior (TPB: Ajzen, 1991). Ajzen was generous in allowing others to expand the framework to allow for additional factors. The original works well with simple networks involving caregivers and patients in exploring aspects such as antimicrobial compliance. In more complex networks, with many more salient others and competition such as in large scale agricultural businesses, the additional aspects explored by our group included: 1) strength of behavioral beliefs, moral norms and duties arising therein, and trust and confidence in others (e.g., competitors) to do what they say they will do under non-regulatory (i.e., voluntary) settings. For stewardship to extend beyond simply following product labels these additional factors need to be taken into considerations and ways to improve and maximize these factors explored.

I have a moral duty to use antimicrobials as therapy

Level of respondent agreement with the statement:
I have a moral duty to treat acutely ill feeder cattle with antimicrobials



Graphs by respondent type

Responses do not differ at $P = 0.413$

This figure illustrates the very strongly held moral conviction by both veterinarians and producers that acutely sick cattle under their care in feedlots must be treated with antimicrobials. Other categories of use are less strongly motivating (e.g., prevention) and thus provide greater opportunities to explore avenues to reduce overall use.

The ‘economies’ of antimicrobial use

- Monetary economics
 - Cost/benefit
 - ‘Perceived behavioral control’
- Political economy
 - Regulations, patent law
- Moral economy
 - *“How economic activities of all kinds are influenced and structured by moral dispositions, values and norms”* (Lancaster University)

The future: towards building resilience

• *Laissez les bons temps rouler?*

or...

• Prepare for a future with?

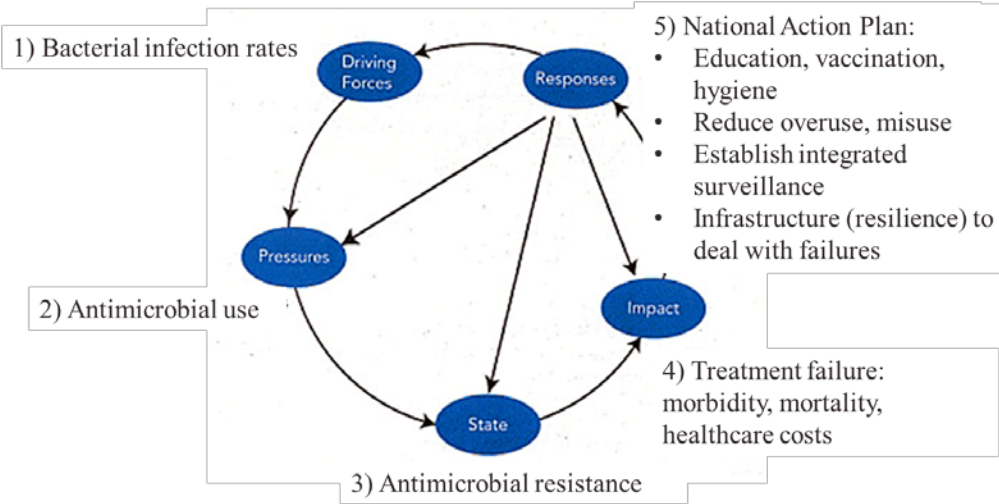
- Less antimicrobial effectiveness
- Fewer new drugs
- Increased demand (population)

• Promote 'virtuous' cycles and avoid vicious cycles



The figures represent (left) a classical 2 by 2 factorial experimental trial such as individuals working in the animal sciences are used to employing to find technical solutions. Condominium owners anticipating landfall of a hurricane (Ivan – 2004) that never hit New Orleans. Figure on right side shows path of Ivan. In such a situation, scenario-based risk management is needed since ‘challenge’ studies on this scale cannot (and should not) ever be conducted. The continued rise of antimicrobial resistance poses one such large-scale risk.

DPSIR Framework: European Environmental Agency



POLICY FORUM

Antimicrobial resistance: The complex challenge of measurement to inform policy and the public

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The figure on the left is the DPSIR framework (drivers, pressures, state, impacts, responses) adapted from the European Environmental Agency (EEA) and applied through work by Wernli et al (PLoS Medicine 2017) to the situation of antimicrobial resistance. Most stewardship programs focus on reductions in pressures (P); on the other hand, a more holistic approach (response) to stewardship in animal agriculture should extend into factors that can also modify driving forces and affect states and their impacts.

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