Institute for Healthcare Improvement

International Forum on Quality&Safety in Healthcare Gothenburg

How Public Health and Scientific Improvement Controlled Malaria and Helped Win WWII

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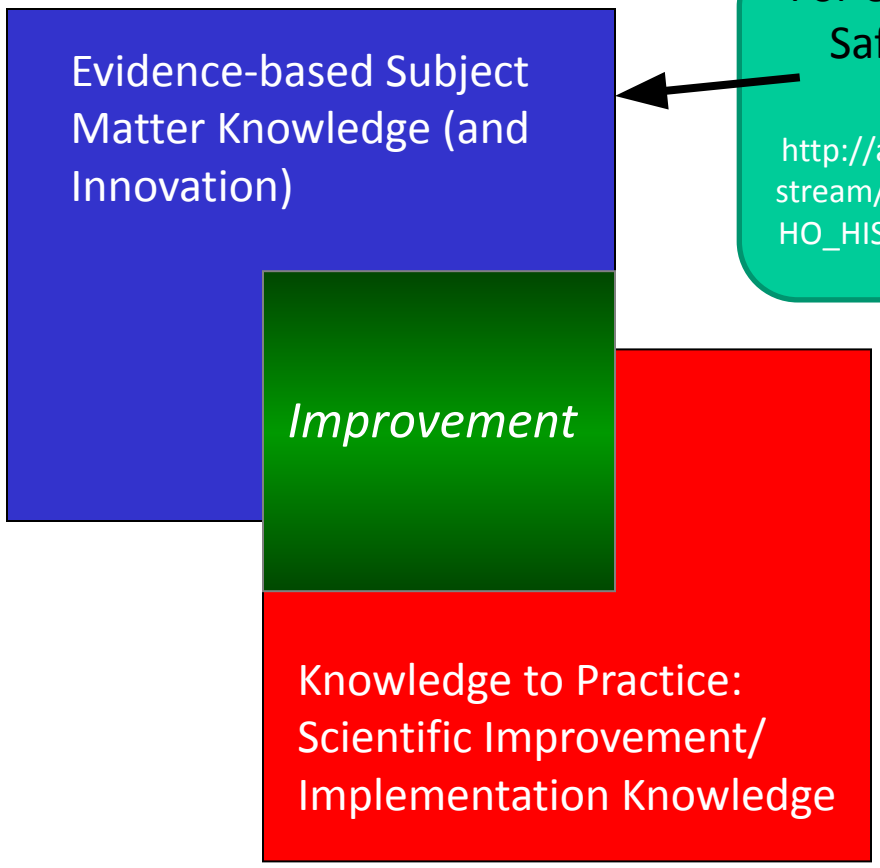
Implementation and Scale-up: Learning from Public Health

- Roadmap
  - Examine how major public health problems have been addressed through:
    - Applying available evidence in practice
    - Real-time experimentation and learning
    - Context-sensitive implementation, and
    - Context-sensitive scale-up
  - Case studies
    - Smallpox
    - Guinea worm
    - Malaria
  - When I discuss approaches to controlling these diseases, ask yourselves if there is a QI analogy. Can you envisage a bundle?
  - Breakouts, polls

All Improvement Requires Bringing Together Two Types of Knowledge

The "what"



For example, WHO Safe Childbirth Checklist
http://apps.who.int/iris/bitstream/10665/199179/1/WHO_HIS_SDS_2015.26_eng.pdf?ua=1

The "how"

Public Health Milestones in Combatting Communicable Diseases

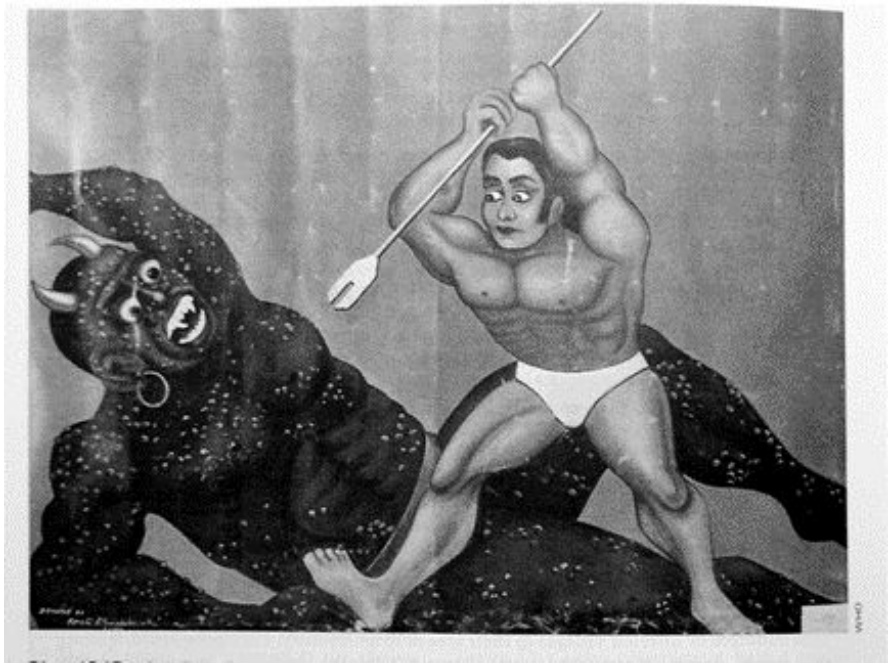
- Smallpox
- Guinea worm
- Malaria
- (If we had the time, we could discuss other examples, such as polio, which has been on the verge of eradication)

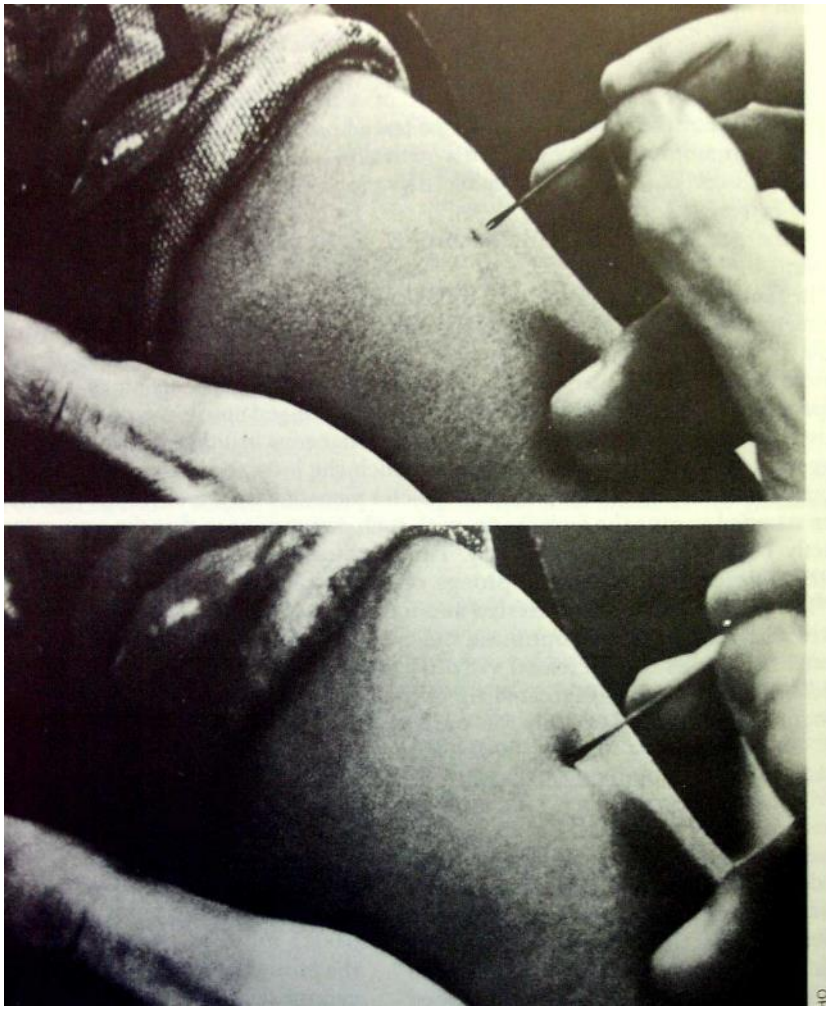
All of these amazing achievements were made without reference to improvement science *per se*, or its Deming and other founders. A key question: Were they using similar methods but with different terms, and/or are there different concepts we should consider?

Smallpox Eradication

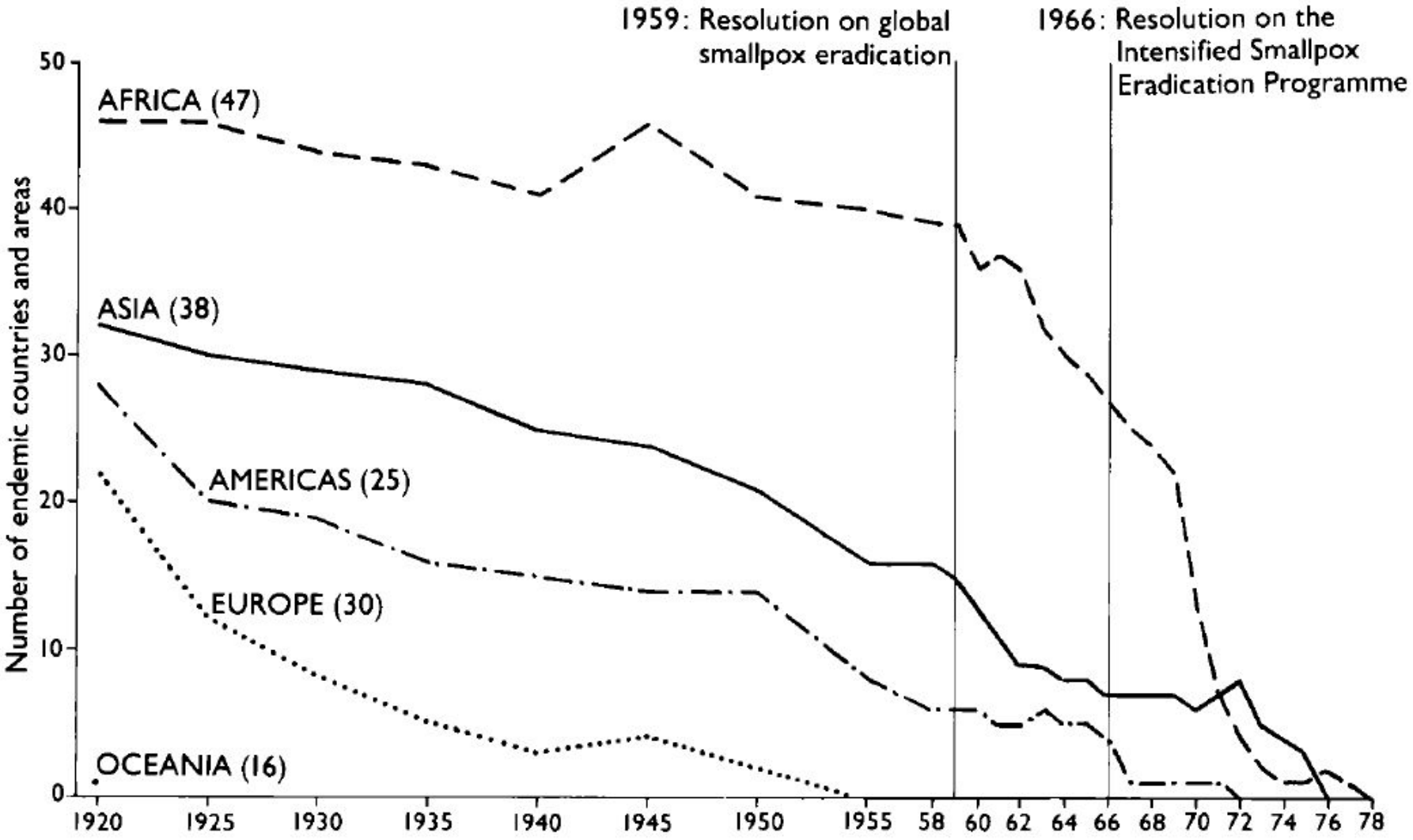
- By the end of Word War II, smallpox had been all but eliminated in many parts of the world. Could it be eradicated?
  - Smallpox uniquely has only one host and reservoir – humans
  - Rash easily recognized
  - Long incubation period
  - No asymptomatic or pre-symptomatic transmission
  - Wide availability of highly effective, standardized smallpox vaccine
  - (*COVID has none of these properties*)
- WHO resolved to eradicate smallpox in 1959
  - At first, the program moved slowly.
- Then WHO ramped up an "intensified eradication program" in 1966
  - Extensive international fund raising
  - Scaled-up use of the proven potent vaccine
  - Donald Henderson put in charge (authoritative, dogged champion)
  - Intensive surveillance and "ring" vaccination when cases detected
  - Teams using *standardized approach* but with *adaption for local context* (culture, religion, conflict
  - Innovation: bifurcated needle

Simple, but Critical Innovation: The Bifurcated Needle

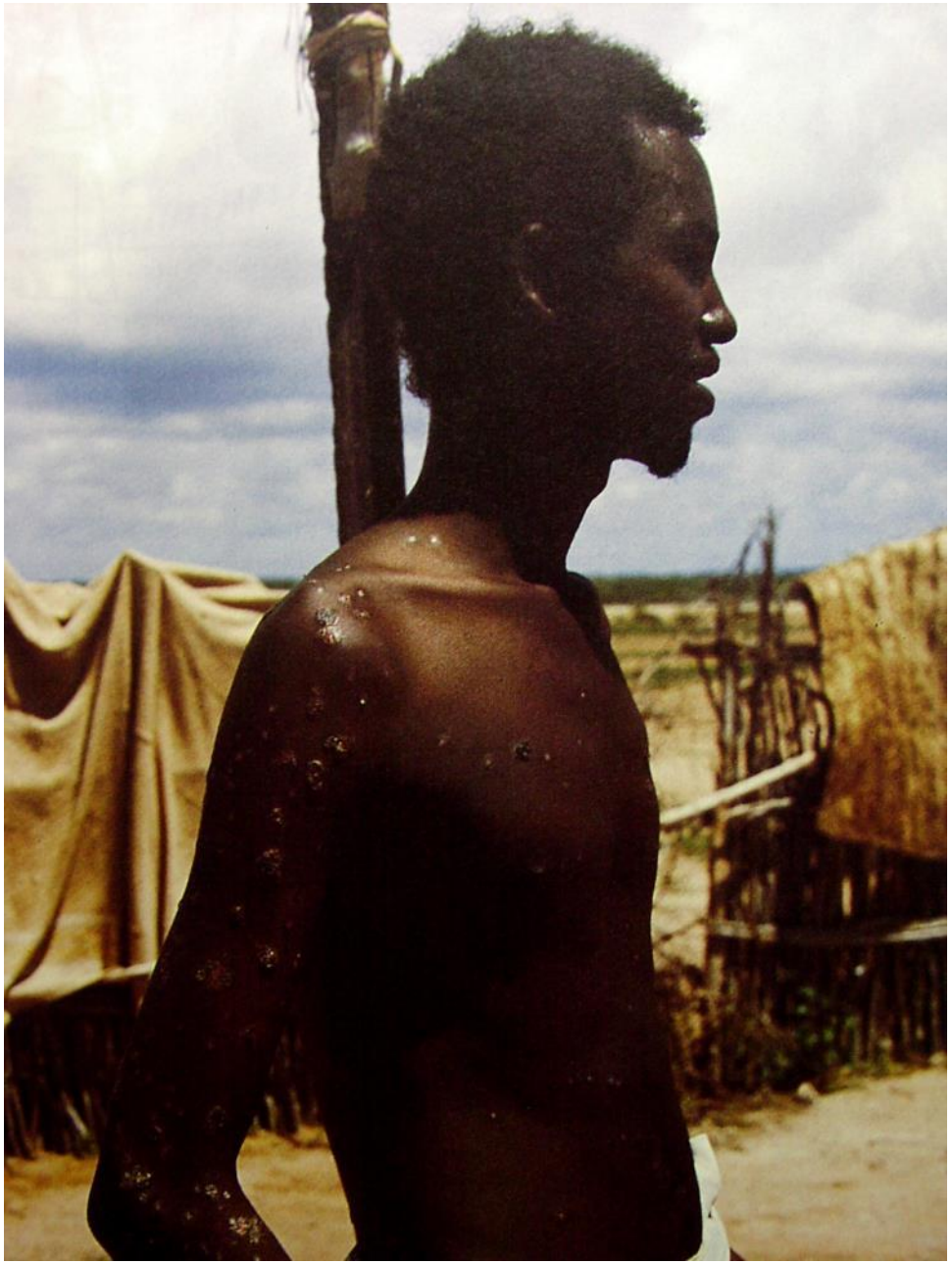




Smallpox Control Timeline



The Last Case 1978

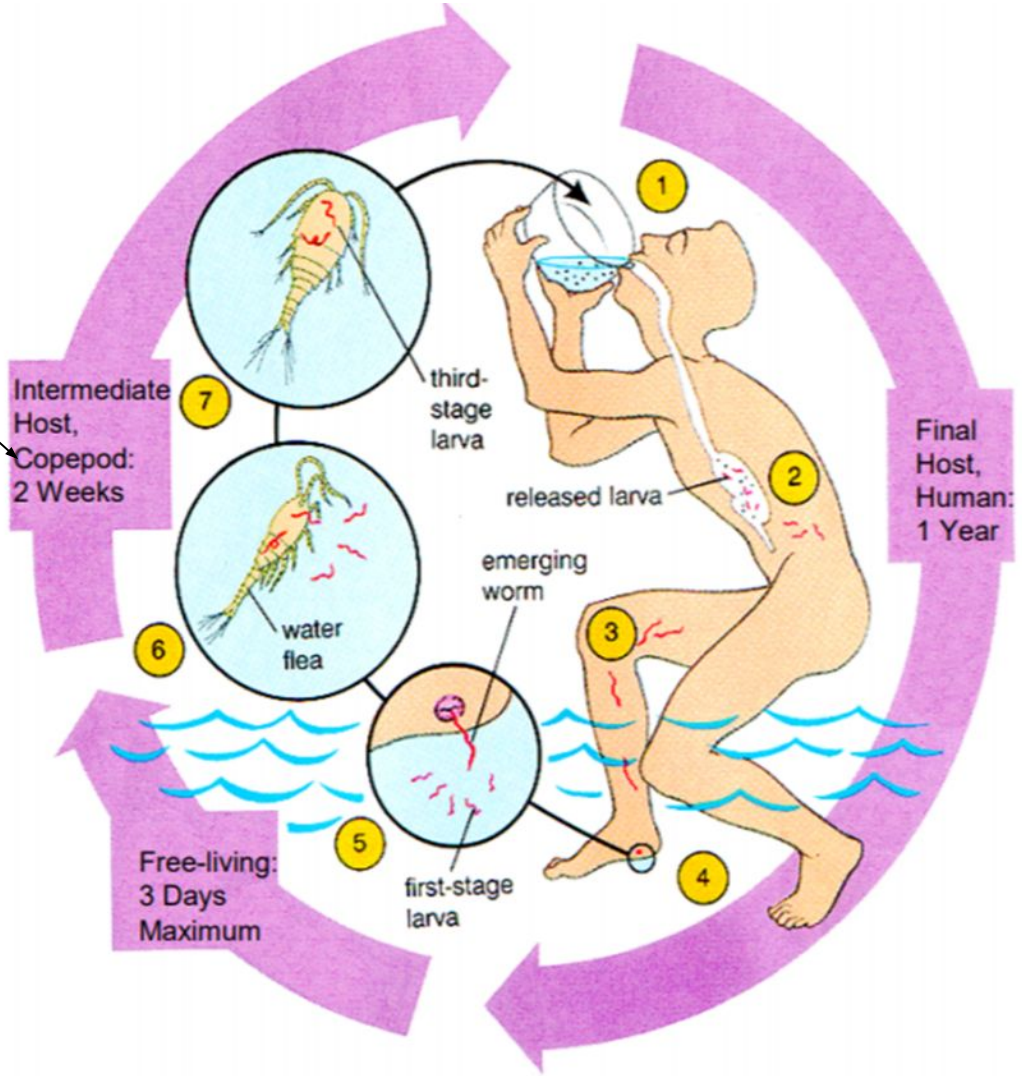


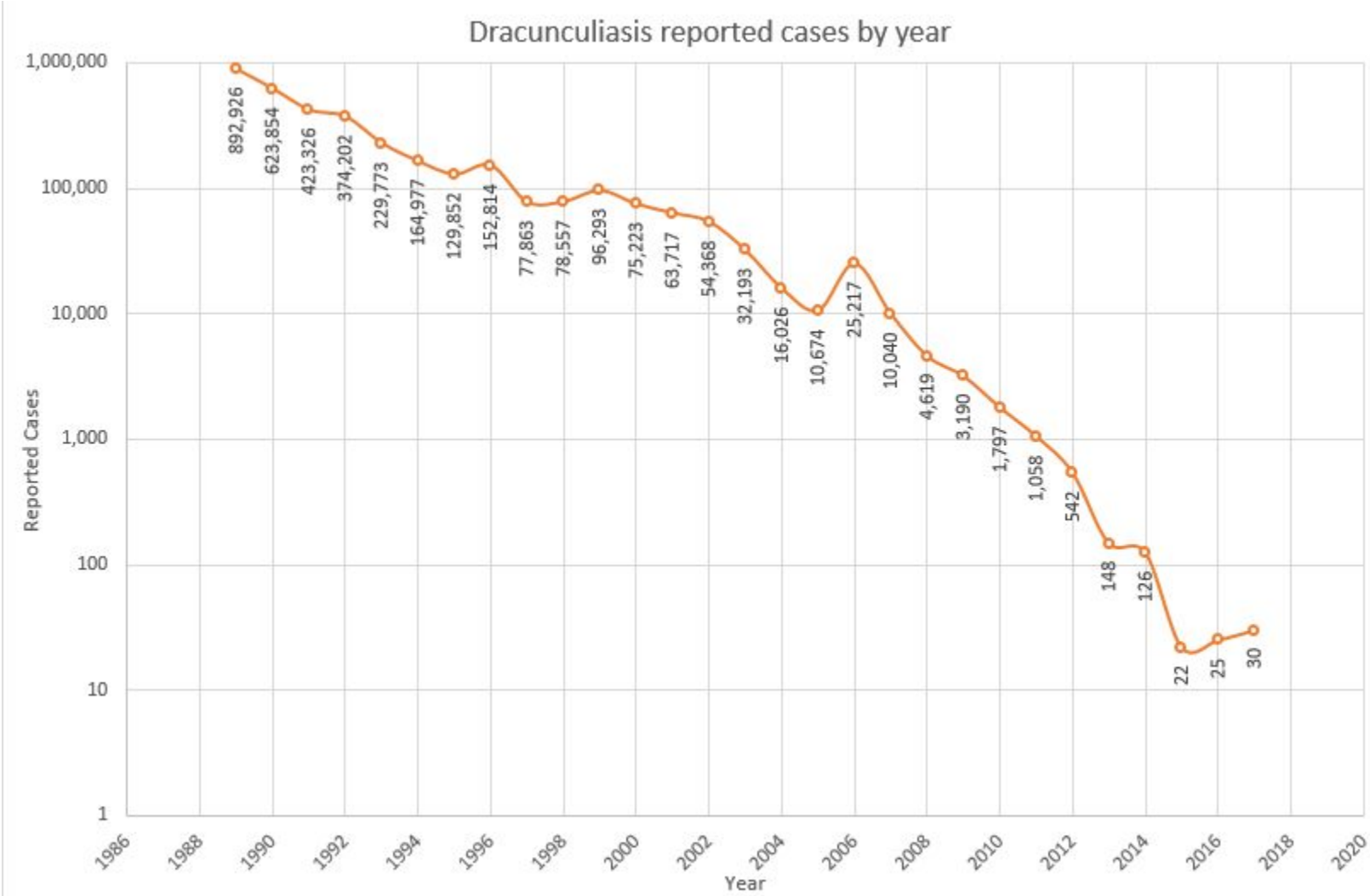
Dracunculiasis (Guinea Worm)

1986: 3.5 million cases, 21 countries Africa and Asia

Dracunculiasis (Guinea Worm) Life Cycle

Copepod is a small crustacean in fresh or salt water





49 cases in 2019, mainly in Chad; other endemic countries S. Sudan, Ethiopia, Angola, Mali. 24 cases 2020, 14 as of 11/2021. Eradication target 2030 now that dog-human transmission verified.

Key Program Elements

- Ministry of Health support
- Funding from Carter Center and others
- Facilitated detection (pictures of the distinctive clinical findings, name for the disease in many local languages)
- Surveillance and real-time data review
- Education and mobilization: community-based volunteers and field supervisors (strong *dose*, large *reach*, good *fidelity*, contextual *adaptation*)
- Frugal innovation: cloth filters for drinking water; protected wells; water from streams
- Avoiding emersion in bodies of water when worm emerging
- Abate (temephos, larvicide for contaminated bodies o
- Deworming animals

Education– Don’t Go in the Water!

Behavioral Economics

- Leveraging behavioral economics rarely done in QI, but increasingly used in public health
- Dogs remain a reservoir for guinea worm, especially in Chad
  - Cash rewards (“cash transfer”) for reporting infected dogs and keeping them way from water sources
- Education to bury discarded fish and entrails (contaminated with guinea worm larvae)

Malaria

Quick Poll

- Malaria is a:
  - Virus
  - Bacterium
  - Protozoan
  - Fungus
  - Free-living amoeba

Quick Poll

- Malaria is transmitted by:
  - Aedes mosquitoes
  - Anopheles mosquitoes
  - Tiger mosquitoes
  - Ticks
  - Person-to-person by contact transmission

Quick Poll

- The most lethal type of malaria is:
  - *P. falciparum*
  - *P. vivax*
  - *P. malariae*
  - *P. ovale*

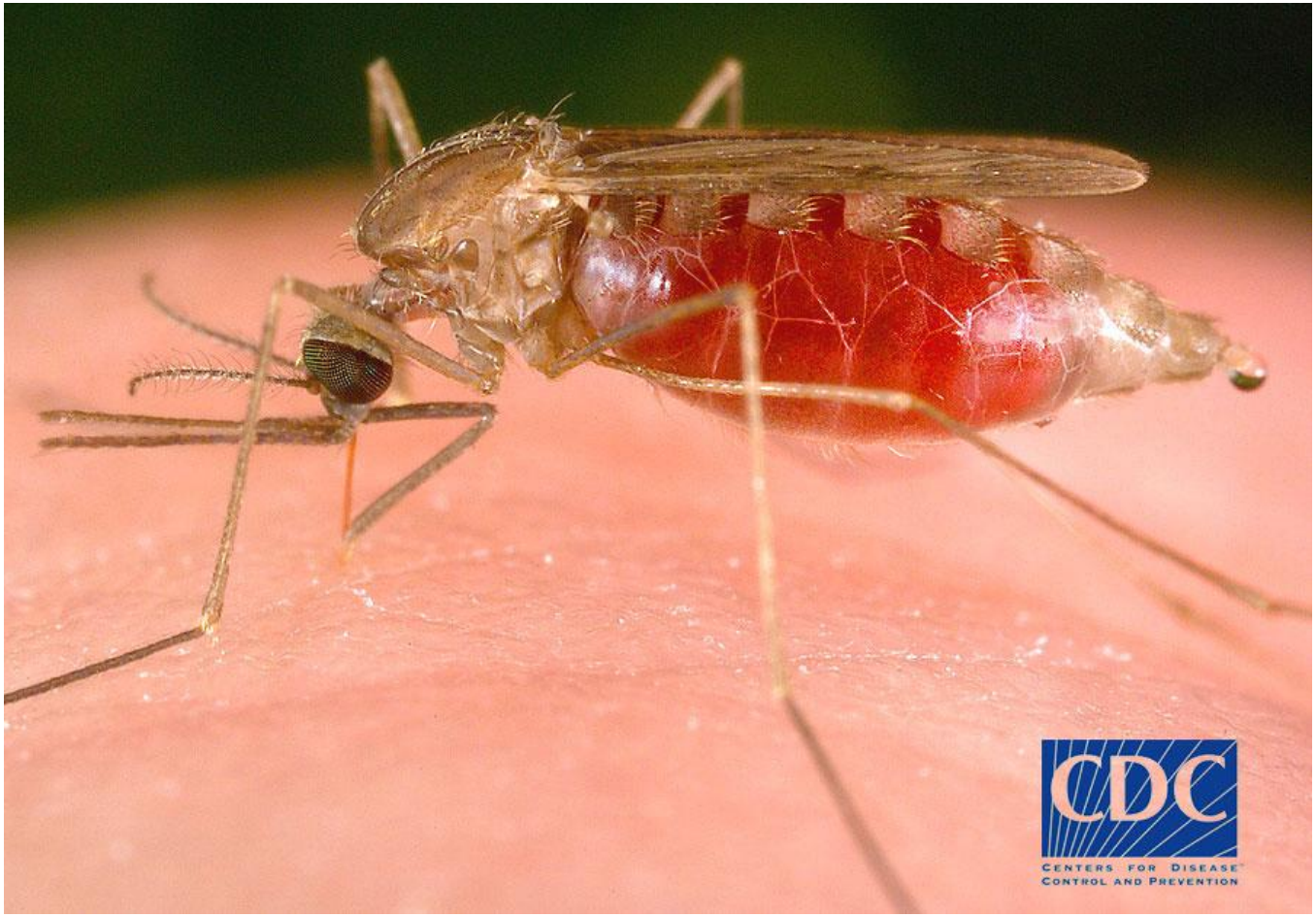
Quick Poll

- Malaria caused approximately how many deaths per year prior to COVID-19 (mortality increased during the pandemic)
  - <25,000 thanks to amazing new pharmaceuticals
  - 100,000
  - 250,000
  - 600,000
  - 1 million

Malaria is a Plasmodium

- A unicellular protozoan (others include ameba, giardia, etc.)
- An obligate parasite of vertebrates and insects
- Typically, an infected insect (mosquito) takes a blood meal from a vertebrate and concurrently injects the parasite, which replicates in the host and completes its life cycle when another insect takes a blood meal
- Parasitizes red blood cells, where it multiples and ruptures red blood cells, leading to “hemolytic” anemia

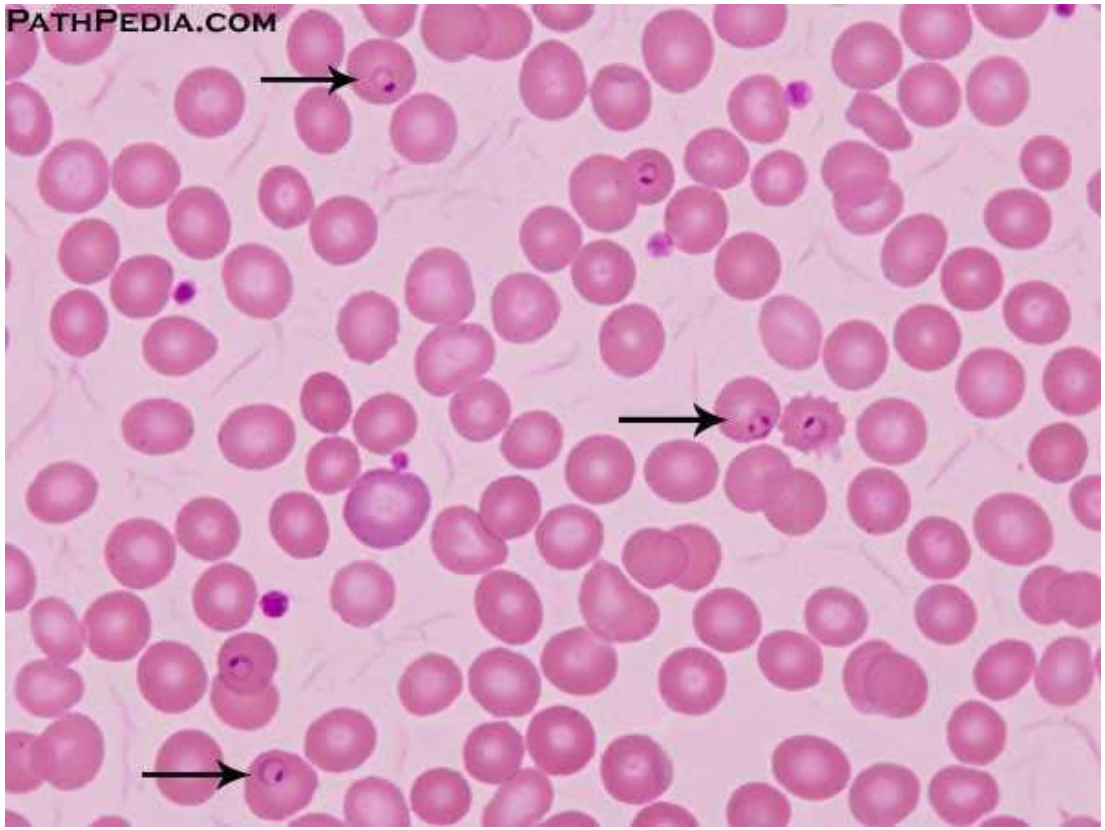
Anopheles Mosquito



40 species can transmit malaria

Most active dusk and dawn

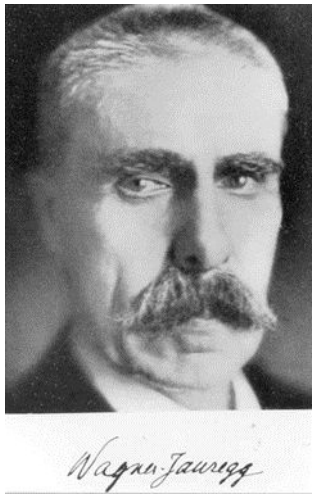
Blood Smear with *P. falciparum* Ring Forms in Red Blood Cells

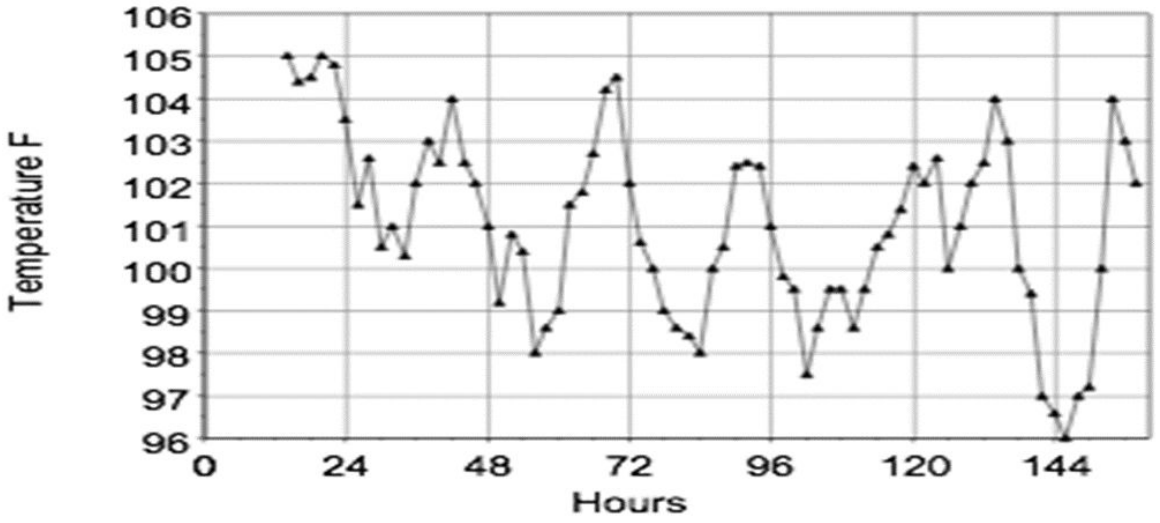


More convenient than microscopy: 15-minute rapid point-of-care diagnostic test detects Plasmodium antigens in blood. Suitable for use in the field

Types of Human Malaria

- *P. falciparum* is the killer
  - Cerebral malaria, “blackwater fever”
  - Cycles of chills, high fever, intense sweating
  - More likely to be resistant to malaria drugs

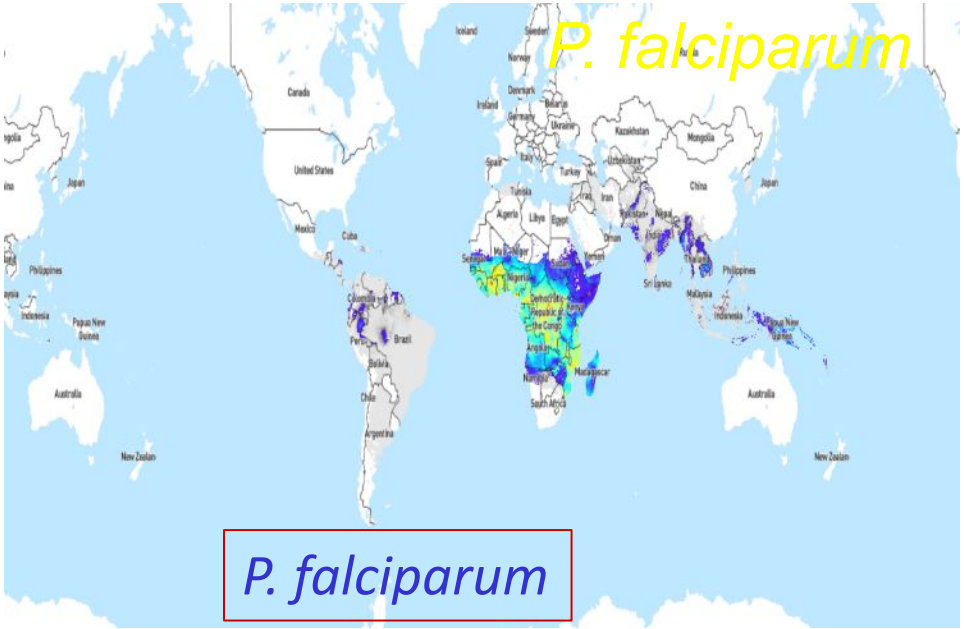


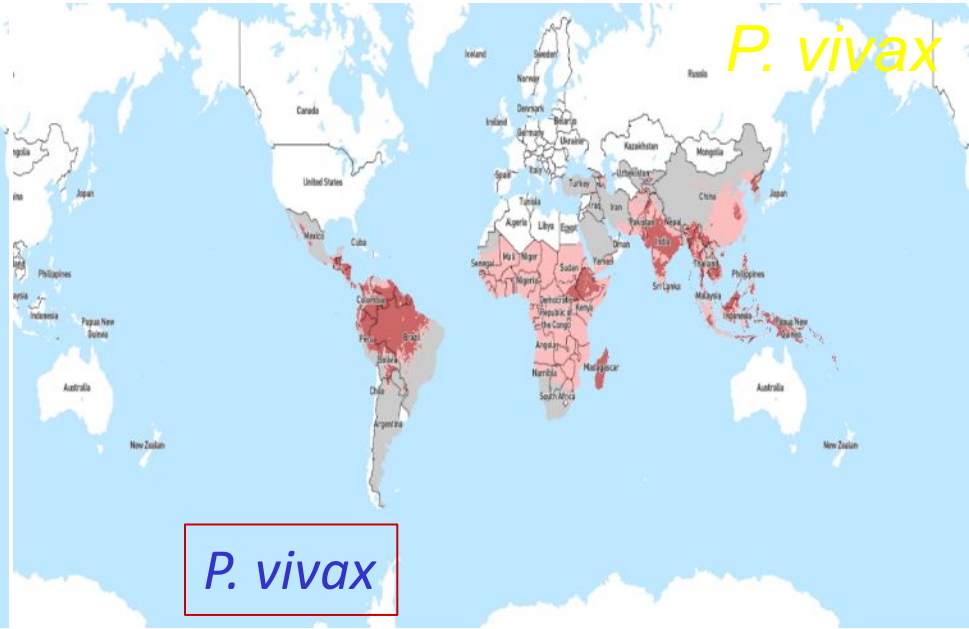


Other Types of Human Malaria

- *P. vivax* can be lethal, but more likely to be chronically debilitating
  - More widespread; found in temperate and colder climates because it hangs out indefinitely in the liver, and mosquito eggs overwinter
  - Requires "Duffy antigen" on the surface of cells to invade red blood cells, so prevalence much lower than *P. falciparum* in Africa where Duffy antigen is uncommon
- Other types: *P. malariae, ovale, knowlesi*
- Sickle cell disease and G6PD deficiency are partially protective
- Mortality higher in exposed people who have not lived in endemic areas

Epidemiology of Malaria





- Nearly half the world's population lives in malaria endemic areas
- 241 million malaria cases, 627,000 malaria-related deaths worldwide in 2020 – a sharp increase attributed to COVID disruptions after decade-long declines
  Vast majority of deaths in Africa, most in children, and due to *P. falciparum*
- Malaria in pregnancy has particularly severe effects for mom and baby
- Major cause of chronic anemia

Strategies to Control Malaria Transmission

Breakout:

What key drivers or major change concepts would you consider in trying to prevent malaria in people living in an endemic area in Africa?

Discuss at tables to start generating your ideas before I share the strategies used in public health to control malaria in resource-limited settings

Direct Mosquito Control Usually is the Most Effective Measure to Prevent Malaria Transmission

Larva Control

Larvivorous fish
"Paris green", petroleum smothering,
Bacillus bacteria

Adulticides

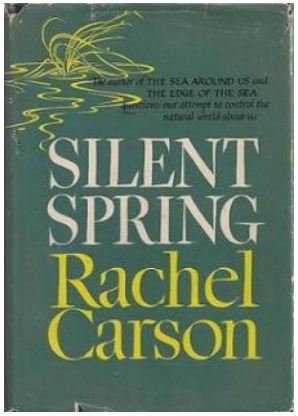
DDT
Indoor residual DDT spraying
(Anopheles mosquitoes rest indoors)

Genetically altered mosquitos?

Gambisoa

T

- DDT discovered as insecticide 1939, 1st used late in WWII
- Persists and accumulates in the environment through food chains
- Toxic, especially to birds (eagles)



Indirect Mosquito Control is a Critical Companion to Direct Methods, Drug Treatment, Vaccines

Bed Nets

Insecticide-Treated Nets (ITNs)
Now double insecticide due to resistance

Secure housing, screens

Avoiding outdoor activities
dusk to dawn for night biters like Anopheles

Protective clothing, Repellants

Malaria Treatment and Prophylaxis

- Quinine (First effective treatment)
- Atabrine (Toxic drug used in WWII)
- Chloroquine (Cheap, effective treatment and prophylaxis where malaria is still sensitive to the drug)
- Mefloquine (Prophylaxis; use declined due to CNS effects)
- Atovaquone-proguanil (Malarone) (Primary prophylaxis drug today)
- Primaquine (Cures parasites that remain in the liver)
- Artemisinin-based combination therapies (ACTs)
  - Artemether with lumefantrine (Current preferred treatment where there is drug resistance)
- Rapid increase in resistance to new regimens!

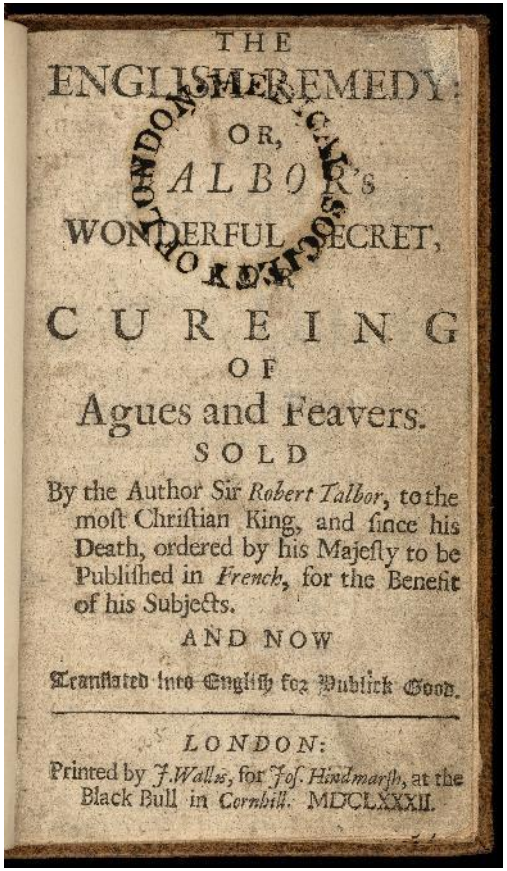
Poll

- Where do you think the effectiveness of quinine was discovered, leading directly to its use in treatment?
  - German pharmaceutical industry (Bayer AG)
  - US pharmaceutical industry (Merck)
  - Peru
  - Indonesia
  - China

Early Treatment of Malaria

- Jesuit Brother Agostino Salumbrino (1561–1642) observed Peruvian natives use of bark of the cinchona tree for shaking chills; “fever tree bark” - quinine
  - Highly valued Cinchona powder taken from Peru
  - Eventually Cinchona “plantations” established in Indonesia and elsewhere

Quinine and the 16th-17th Century Little Ice Age (Peak 1570s-1730s)



THE
ENGLISH REMEDY:
OR,
ALBOR's
WONDERFUL SECRET,
CUREING
OF
Agues and Feavers.
SOLD
By the Author Sir *Robert Talbor*, to the most Christian King, and since his Death, ordered by his Majesty to be Published in *French*, for the Benefit of his Subjects.
AND NOW
Translated into English for Publick Good.
LONDON:
Printed by *J. Wallis*, for *Jos. Hindmarsh*, at the Black Bull in *Cornhill*. MDCLXXXII.

Wellcome Institute for the History of Medicine
1682

Hunters in the Snow, 1565
Peter Brueghel the Elder
Kunsthistorisches Museum

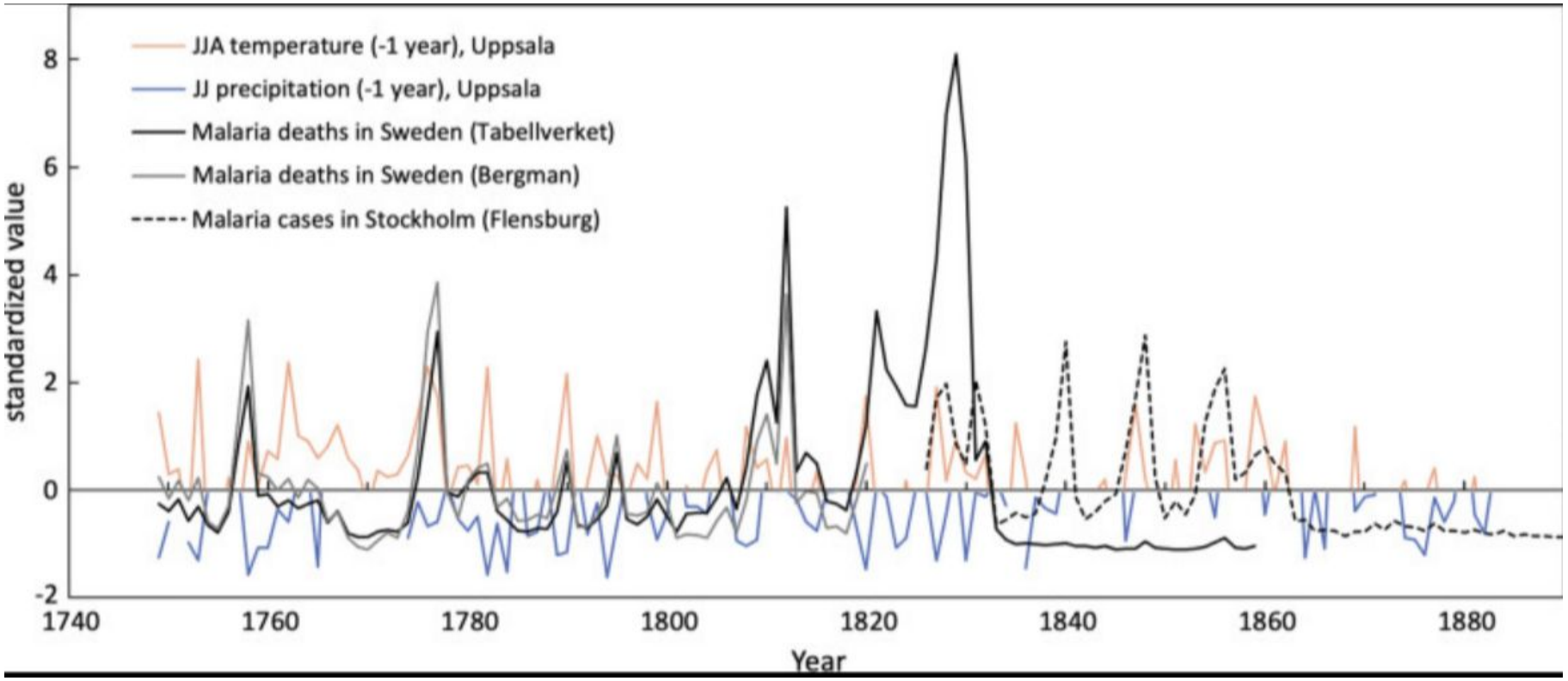
https://wwwnc.cdc.gov/eid/article/6/1/00-0101_article

Historical Malaria in Sweden

The spatial distribution of annual malaria-attributed deaths at parish level in Sweden. Each circle represents annual malaria-attributed deaths reported at a parish level 1749–1859. The size of the circle reflects the number of death cases

•Chen TT et al. The spatiotemporal distribution of historical malaria cases in Sweden: a climatic perspective. Malaria Journal DOI: 10.1186/s12936-021-03744-9

Impact of Climate



Time-series of malaria datasets against climate variables. Malaria datasets from three data sources (Tabellverket 1749–1859, Bergman 1749–1820, Flensburg Stockholm 1826–1890) and the relations to meteorological data.

Poll:

The British Occupiers of India during the Raj liked to gather in their clubs for gin and tonic. Do you think that this was effective in reducing the severity of malaria?

Yes/No

An Ancient Disease

15-20 million-year-old mosquito *Culex malariager*, was discovered in the Dominican Republic preserved in amber. Oldest known fossil showing *Plasmodium* malaria, related to the type that today infects humans. (Photo by George Poinar, Jr., courtesy of Oregon State University)

A Brief History of Malaria

- ~ 2200 BCE “swamp fever” mentioned in Egyptian papyrus medical texts
  - DNA confirms presence of malaria in the time of the Pharos
  - 5th Century BCE, Herodotus alludes to malaria and its treatment in ancient Egypt
  - Cleopatra slept under a mosquito net
- ~ 400 BCE: Hippocrates described splenic enlargement and three different fever patterns (quotidian, tertian, and quartan)
- ~ 400-300 BCE: Discussion of epidemics of “paroxysmal fevers” and enlarged spleens in the Chinese *Nei Ching* (The Canon of Medicine)

Malaria History

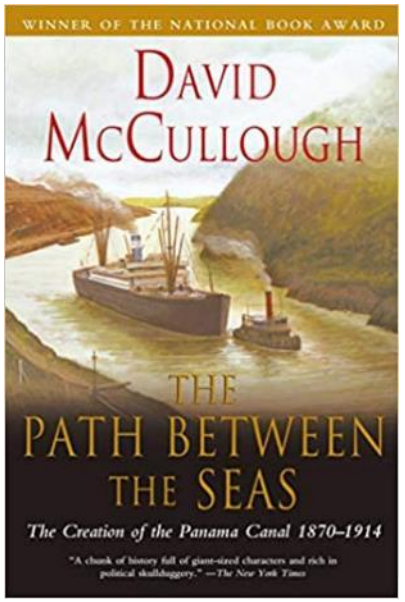
- Roman Empire endured annual outbreaks, mainly in area of Pontine Marshes (Poor Hannibal in 2nd Punic War!)

  - Malaria may have contributed to end of Western Roman Empire
- 17th Century Europe – "Ague" and "marsh fever" because of proximity to marshes
- Colonial America – decimated early colonialists and, like yellow fever, was a major impetus for the slave trade
- 1880: French physician, Charles Louis Alphonse Laveran, identified malaria parasite in blood from patients in Algeria
- 1897-98: British physician, Ronald Ross, described the role of mosquitoes in the transmission of malaria

Building the Panama Canal

- The French had tried to build the canal
  - Ferdinand de Lesseps had built the Suez Canal, proposed sea-level Panama Canal
  - 1880-89: billions of Francs, 125,000 people (you know who did the work!) Gave up, largely due to malaria + yellow fever
    - De Lesseps found guilty of mismanagement, son went to jail
- Panama Canal, 1904-1914
  - Complicated politics, but approved by Teddy Roosevelt using route through Panama (some preferred Nicaragua)
  - Malaria known to be mosquito-borne, Reed had recently found same for yellow fever (different mosquitoes)
  - Not translated into early work on Canal
  - William Gorgas to the rescue

    (remember, no DDT yet)



William C. Gorgas

Malaria Elimination Campaigns: What was Learned in Italy

- Pre WWI: The failed quinine treatment strategy
- Post WWI and lessons learned and not learned

Malaria in Italy

Pontine Marshes 1860s

Italian Eradication Efforts Early 19th Century

- Unification of Italy led to massive infrastructure projects (railroads), deforestation
  - Driven by Northern Italy (*vivax* predominant); Southern Italy poorer and agricultural (mainly *falciparum*)
- Lots of mosquito-breeding areas: marshes, rice fields
- Innovative research by Giovanni Battista Grassi, including human research at Santo Spirito and discovery of malaria life cycle
- Campaign launched by Prime Minister Giovani Giloitti
  - At first reliance on mass quinine treatment
  - But poor access to care, complex regimen with side effects, poverty, illiteracy, lack of understanding
  - Transitioned to education, better housing, trade union support, social programs to address poverty
  - From “magic bullet” to a *comprehensive population-based approach*, leading to dramatic decline in malaria
  - All undone by WWI

Mussolini's Malaria Eradication Campaign

- Decided on demonstration project in Pontine Marshes even though only 1000 people lived there
  - Drainage
  - Settled the land
  - Bult better housing with screens
  - Education starting with youth
  - Propaganda
  - Massive decrease in risk (baseline was 80% risk of malaria spending one unprotected night in the Marshes

The Pontine Marshes Before Land Reclamation

https://www.youtube.com/watch?v=_CZFyY1n72o

Impact of Malaria on the War in the Pacific and North Africa, 1941-45

Key Issues in WWII Pacific Theater and other Malarious Conflict Regions

- More troops out of commission from malaria than wounds
  - 60-65% of troops in Pacific Theatre experienced malaria
- Key logistical and supply hubs, such as Accra, Ghana and Fisherman's Lake, Liberia incapacitated, with virtually 100% of Pan Am employees and military infected
- Treatment challenges (Dutch East Indies occupied by Japan so quinine scarce), atabrine toxic
- "The Malaria Project" (like the Manhattan Project)
  - Controlling mosquitoes and protecting troops
  - Developing new, more effective, less toxic drugs

Atabrine

- Atabrine (8-aminoquinoline)
  - Developed by IG Farben and Bayer in Germany from yellow dye (? What else did IG Fraben make?)
    - Patent and supply issues with Winthrop, US supplier
  - Toxic and avoided by troops
    - Vomiting, diarrhea, yellow skin, severe skin disease, depression and “psychosis”

Breakout

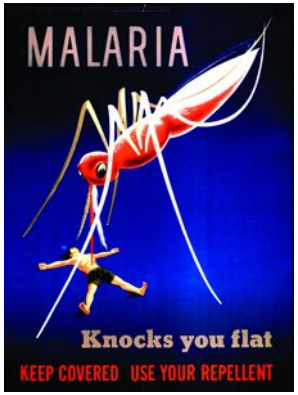
- You are summoned to design a program to control malaria in Ghana and Liberia because you are experts in improvement science
- Assuming what was known in the early days of WWII (no DDT), how would you design this control program?
  - You may want to specify the main “drivers” that you think, will reduce transmission
- Draft a charter for your initiative, including members of the team and their primary responsibilities

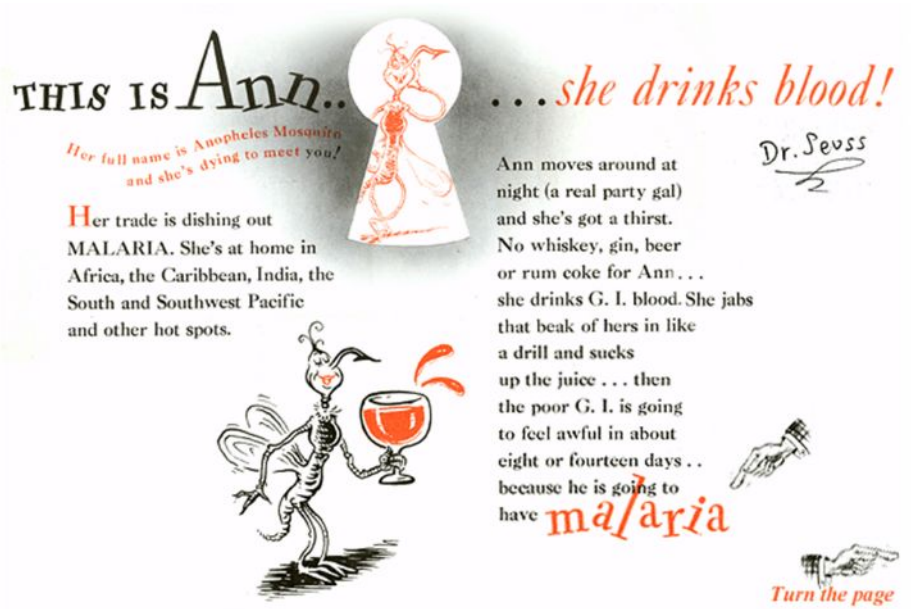
Mosquito Control

- Lowell Coggeshell, training programs, mosquito squads
- Success in Accra (virtual elimination):
  - Randomized controlled trial, Pan Am v. British
    - Quinine v. bed nets, screens, permethrine spraying
    - 87/100 v. 1/60 (he sneaked out at night)
  - Education and behavioral science
  - African workers in separate quarters >1 mile away (same for sex workers)
  - Protective clothing
  - Screens and bed nets
  - Drainage
  - Larva mitigation (engine oil, kerosene, Paris Green dye)
- Similar strategy eliminated imported *A. gambiae* in Brazil

Behavior Change

- Dr. Seuss (Theodor Geisel) and other “marketing” campaigns
- Adapated to context (Liberia v. Ghana)





Private Snafu vs. Malaria Mike
Snafu (situation normal all “fouled” up)
https://www.youtube.com/watch?v=y9mLM1K3U2s

Sustainability Issues

- Rapid deterioration in Liberia
- Disciplined approach to mosquito control and personal protection abandoned
- Venereal disease rampant as a result of relations with local women ("bush girls"), usually at night
  - Controlled villages, Shangri-La and Paradise, established more than 1 mile away and with rigorous checking for venereal disease
- Malaria largely controlled again

https://www.lastwordonnothing.com/2014/10/22/8696/

Mosquito Control in the US

- Office of Malaria Control in War Areas responsible for controlling malaria around US military bases
- 1946 Communicable Disease Center (CDC) established to eliminate residual malaria in 13 Southeast US states
  - DDT spraying, including 4.65 million houses sprayed
  - Drainage, elimination of breeding sites
- US declared malaria-free in 1949

Public Health Applied the 4 Pillars (Deming's Profound Knowledge "Lenses") of QI without the Terminology

- Epistemology: Rapidly learning through testing and experimentation
- Appreciation of Systems: Where they are vulnerable, need monitoring, and need to be highly reliable
  - AKA, failure mode and effects analysis
- Variation: Looking at data over time to gauge improvement and variation in outcomes
- Psychology and behavior change

What was Unique or Rigorous

- Widely acknowledged burning platform
- Very ambitious, widely embraced, goals
- Strong, broad will to succeed
- Adequate, consistent funding
- Charismatic (or at least very effective) leadership/champions
- Command and control with consistent messaging
- “Hard edges” and accountability
- Population-based approach
- Planning for scale-up from day 1
- Clear, standardized core elements coupled with agile adaptation to context
- Real time data
- Sophisticated, diverse behavior change approaches

A Final Plea to Improvers: Respect and Learn from Other Scientific Disciplines

- Behavioral science and behavioral economics
- Network science
- Data mining , AI, and advanced data analytics
- Qualitative/ethnographic research
- Economics
- Epidemiology
- Information science
- Translational science
- Public health

“Malaria Project” Ethical Issues that Resonate Today

- Tension between external necessity and ethical experimentation
- Recognizing that the concept of “ethical human experimentation” and “ethics review boards” were largely products of the WWII experience

Remember, there was an Urgent Need for Drugs to Replace Quinine (Unavailable) and Atabrine (Unacceptably Toxic)

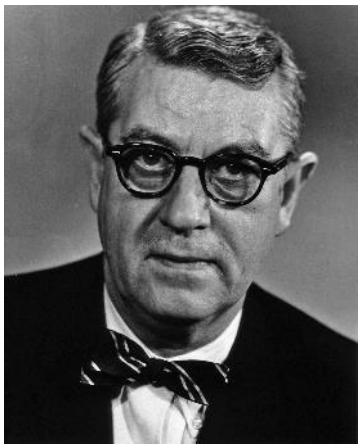
- Massive, well-funded Malaria Project to screen compounds for efficacy against malaria and safety
- The Malaria Project ultimately used human studies to evaluate efficacy and toxicity of drug candidates
  - Patients with neurosyphilis, schizophrenia and other serious mental illness, and prisoners

Breakouts

- What constraints would you recommend for performing these experiments given that it was wartime?
- Consider the fact that Julius Wagner-Jauregg had received a Nobel Prize for using malaria to treat neurosyphilis, but that other treatments were available
- Assume that these are efficacy and safety clinical trials, not quality improvement programs

Experiments on Patients with Neurosyphilis

- Based on Julius Wagner-Jauregg's studies, "legitimized" by his Nobel Prize
- James Shannon led drug testing "factories" in state hospitals caring for neurosyphilis patients (Goldwater Memorial, Bellevue, Manhattan State Hospitals)
- Expanded from syphilis patients to schizophrenic patients, whom he called "clinical material," or just "material."



James A. Shannon
Director NIH, Presidential Medal for Merit

Malaria drug research at Stateville Penitentiary, Joliet, Illinois

- Stateville design based on Jeremy Bentham's (utilitarian philosopher) 1791 panopticon prison proposal
- "Panopticon" from Greek, for "all seeing." Prisoners all could be seen by a guard but did not know they were being watched, so would tend to regulate their own behavior.
- Bentham wanted the general public to be able to see the guards
- He thought design would apply to other institutions

Stateville Malaria Drug Research

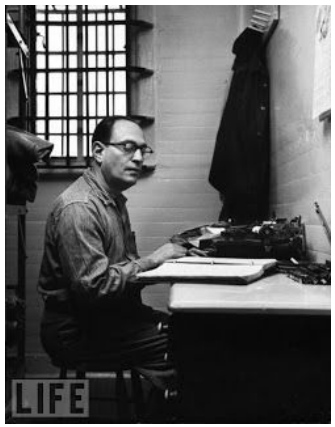
- Research to study less toxic, effective derivatives of German drug, plasmochin (8-aminoquinolones). among others
  - Some produced severe side effects; one prisoner died
  - Later, chloroquine and other drugs tested for long-term effects
  - Primaquine resulted from these studies – a “radical cure” for vivax malaria, but severe hemolytic anemia in black prisoners
    - Black and white prisoners intentionally placed in different groups – white prisoners were cured without anemia
    - Birth of pharmacogenetics

Stateville Malaria Drug Research

- Stateville studies overseen by Alf Sven Alving, a nephrologist, and young doctors from U. of Chicago in the Penitentiary's hospital, with rather light security
- Prisoner "volunteers" served in diverse rolls and constituted the majority of staff and subjects – every role but doctor and nurse
  - Largely responsible for their own security

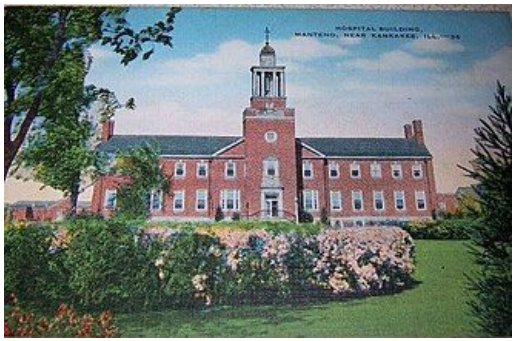
Nathan Leopold and Richard Loeb

- 19 and 18 years-old respectively, enrolled at U of Chicago and from well-to-do families
- Targeted and brutally murdered 14 year-old Bobby Franks
- Clarence Darrow defended them against the death penalty claiming Leopold and Loeb were mentally unstable
- Sentenced to life + 99 years in Stateville Penitentiary
- Loeb stabbed to death in shower, January 1936
- Leopold, an X-ray tech in prison hospital, transferred to malaria experiments
  - Kept detailed logs
  - Urged participation
  - Claimed he was patriotic
- Parole March 1958



Breeding Mosquitoes for Experiments: Manteno State Hospital

- Housed people with serious mental illness and neurosyphilis
- Large typhoid outbreak 1939: 400 cases, 40 deaths
- 1948 U of Chicago archives indicate patients at Monteno were used for maintaining malarious mosquito population
  - Nathan Leopold confirmed mosquitoes from Manteno used at Stateville
  - Jauregg cautioned that malaria fever effective only for syphilis
- Surgeon General at the time was Thomas Parran



Manteno State Hospital
1930-1985

Prisoner Incentives

- Payment
- ? Patriotism in WWII
- Amenities (robes, showers)
- Cards and dominoes
- Better than the rock pile
- Probably underestimated pain, suffering, risk
- Milder punishment, especially early on; fewer confinements in “the hole” (solitary)
- “Prison’s moral elite,” prestige
- Eligible for early parole (malaria part of the punishment)
- Coverage by radio, media (Life magazine)

Nuremberg Trials

- Stateville experiments used to defend perpetrators of Dachau experiments
- Nuremberg Code issued during Stateville experiments but not formally adopted by US and not part of the law
- Stateville experiments almost certainly violated tenets of the Code

The Nuremberg Code

1. Consent must be obtained.
2. “Fruitful results” should be guaranteed.
3. The risks justified by the anticipated results
4. Avoid all unnecessary suffering
5. If death anticipated, experiment should not be done, unless those conducting the experiment participate as subjects
6. Risk proportionate to “humanitarian importance”
7. Adequate preparation and support
8. Conducted by qualified persons
9. Subject should be able to stop the experiment
10. Scientist should be willing to stop the experiment

§46.306 Permitted research involving prisoners

In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

As of July 1, 2021:
https://www.ecfr.gov/cgi-bin/text-idx?m=07&d=01&y=2021&cd=20210708&submit=GO&SID=83cd09e1c0f5c6937cd9d7513160ic31&node=pt45.1.46&pd=20180719#sp45.1.46.c

Breakout Questions

- Considering evolution of standards for research in humans beginning with Nuremberg, and the current advice from US Health and Human Services (Office for Human Research Protections), under what circumstances would you deem research of prisoners acceptable today?