Considerations for typhoid elimination

John A. Crump, MB ChB, MD, DTM&H
McKinlay Professor of Global Health

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Good afternoon.
It is a great pleasure to have the opportunity to speak.
I will spend the next 15 minutes discussing some considerations for typhoid elimination.

Overview

- Definitions and historic prioritization efforts
- Biological and technical factors
- Economic considerations
- Social and political criteria
- Demonstration project

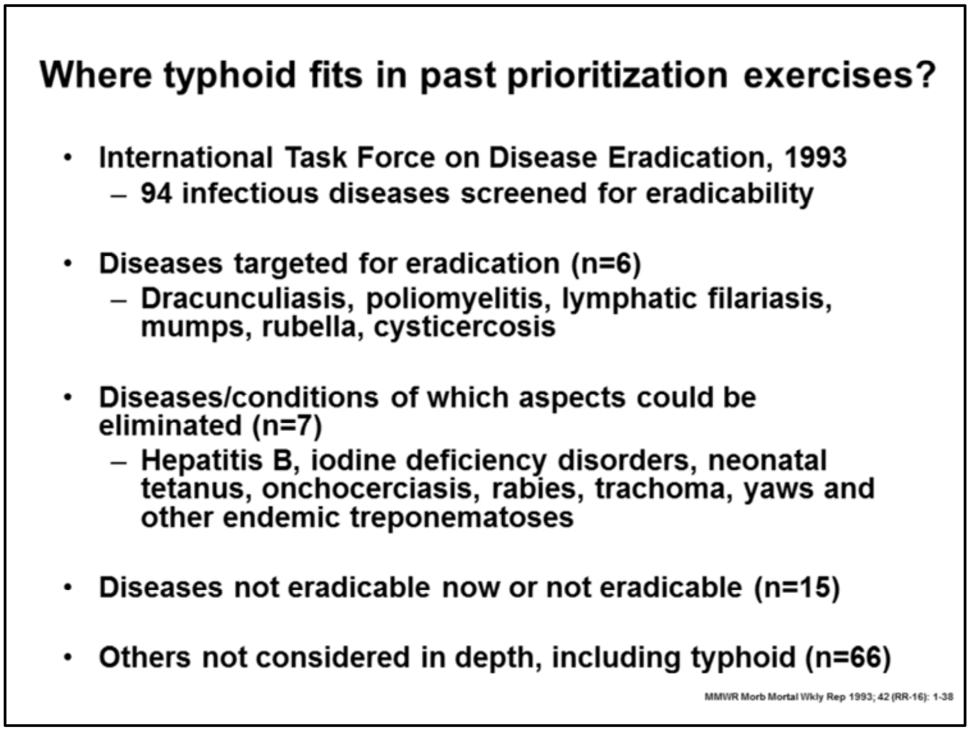
During this talk I will discuss elimination and related definitions, and review historic prioritization efforts on disease elimination and eradication.
I will discussed biological and technical factors relevant to typhoid elimination.
And touch on economic considerations and social and political criteria.
And I will finish with what is probably a reasonable next step; considering an elimination demonstration project.

Definitions: Dahlem Workshop on Eradication of Infectious Diseases, 1997

Term	Definition	Continued intervention required?
Control	Reduction of disease incidence, prevalence, morbidity, or mortality to locally acceptable level through deliberate efforts	Yes
(Elimination of disease as public health problem)	(Reduction to more than zero of incidence of specified disease in defined geographic area through deliberate efforts)	Yes
Elimination of disease	Reduction to zero of incidence of specified disease in defined geographic area through deliberate efforts	Yes
Elimination of infections	Reduction to zero of incidence of infection from specific agent	Yes
Eradication	Permanent reduction to zero of incidence worldwide of infection	No
Extinction	Specific infectious agent no longer exists in nature or the laboratory	No

Dowdle WR, Hopkins DR. The eradication of infectious diseases. Dahlem Workshop Reports. 1997

I wanted to start by reminding ourselves of definitions relevant to this session.
I think that the definitions provided by the Dahlem Workshop on Eradication of Infectious Diseases, 1997, are the most widely accepted.
Here, control is defined as the reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level through deliberate efforts.
I have added the term ‘elimination of typhoid fever as a public health problem’ that was not defined at the Dahlem Workshop and some would argue is really an alternative framing of disease control.
It has been proposed that an incidence rate less than 5 per 100,000 per year, similar to that presently observed in many high-income countries, might be a target threshold for elimination of typhoid as a public health problem.
****CLICK**** This session is on typhoid elimination.
Here it is useful distinguish the elimination of a disease, typhoid, from the elimination of infections with *Salmonella* Typhi.
Elimination of typhoid is reduction to zero of disease incidence in a defined geographic area through deliberate efforts.
Whereas elimination of infectious would include not only a reduction of disease to zero, but also a reduction to zero of infections from *Salmonella* Typhi.
I would flag that a concept in common use that is more difficult to define is the elimination of a disease ‘as a public health problem,’ where control efforts achieve levels of disease that approach but do not reach zero.
As a reminder, eradication extends the concept of elimination of infections from one or more geographic areas to the globe: the permanent reduction to zero of incidence worldwide of infection.
And extinction includes that the infectious agent no longer exists in nature or the laboratory.
Unlike control and elimination, eradication and extinction provide the advantage that the intervention or interventions are no longer required.
While I will be sticking to brief and focusing on elimination, I will at times use the term eradication to reflect the worldwide extension of the concept.



It is worth reflecting on where typhoid fits in past prioritization exercises for disease elimination or eradication.
There have been a number of efforts to develop lists of diseases for elimination or eradication. One of the more prominent was the International Task Force on Disease Eradication that met from 1989 through 1992, publishing its findings in 1993.
The Task Force screened 94 infectious diseases for eradicability as well as several non-infectious conditions.
They identified six diseases targeted for eradication: dracunculiasis, poliomyelitis, lymphatic filariasis, mumps, rubella, and cysticercosis.
And seven diseases or conditions of which aspects could be eliminated: hepatitis B, iodine deficiency disorders, neonatal tetanus, onchocerciasis, rabies, trachoma, and yaws and other endemic treponematoses.
As well as 15 diseases either not eradicable now or not eradicable.
And another 66 that were not considered in depth.
Typhoid was among these 66.

Diseases screened for potential eradicability by International Task Force on Disease Eradication, 1993

Disease/condition	Extent of problem	Epidemiologic vulnerability	Intervention(s) available	Political will	Comment
Typhoid fever	Worldwide; fatality rate up to 10%, 25,000 deaths/year	Human asymptomatic carrier state; drug-resistant strains; diagnosis by blood culture	Hygiene, water, sanitation; antibiotic therapy; partly effective vaccine	None	—

MMWR Morb Mortal Wkly Rep 1993; 42 (RR-16): 1-38

And if you dig through the appendix of the Task Force report, you will find typhoid fever mentioned once with a now outdated estimate of the extent of the problem; vulnerabilities listed as the human aymptomatic carrier state, drug-resistant strains, and diagnosis by blood culture; and interventions available including hygiene, water, and sanitation, antimicrobial therapy, and a partly effective vaccine.

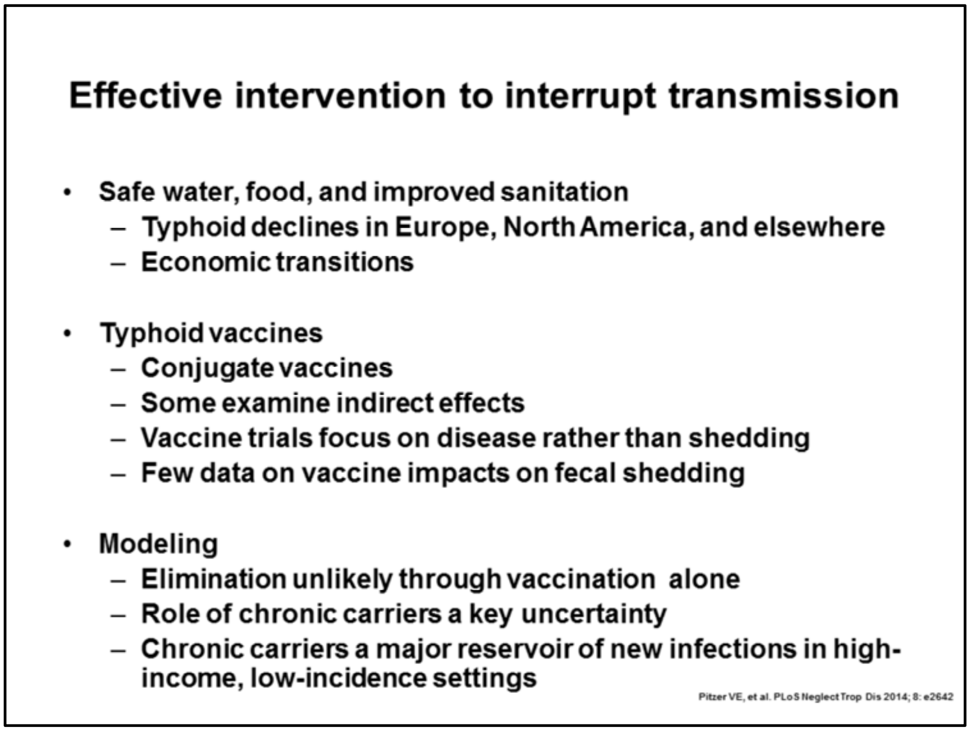
****CLICK**** And notably the political will to eliminate or eradicate the disease was indicated to be 'none.'

So on this somewhat gloomy note, I wanted to take a look at considerations for typhoid elimination more than a quarter of a century later in light of progress and also remaining challenges.

Biological and technical factors

- An effective intervention is available to interrupt transmission of the agent
- Practical diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to transmission
- Humans are essential for the life-cycle of the agent, which has no vertebrate reservoir and does not amplify in the environment

Let's start with biological and technical factors.
Key considerations in this area include whether there is:
An effective intervention is available to interrupt transmission of the agent.
Practical diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to transmission, and
That humans are essential for the life-cycle of the agent, which has no vertebrate reservoir and does not amplify in the environment.



Where are we at with effective interventions to interrupt typhoid transmission?

Well, there is evidence often presented at typhoid conferences that improvements in safe water, food, and improved sanitation were ecologically associated with Europe, North America, and elsewhere a century ago.

And that more recent economic transitions in some countries, including those described by Zulfi Bhutta's Tackling Typhoid project, have also be associated with declines in typhoid fever.

Compared with 1993, the typhoid vaccine situation has improved with conjugate vaccines that protect infants early in life and we hope will protect for longer periods than older vaccines.

We also have evidence of indirect effects of vaccine, with vaccination with older providing a degree of herd protection in some settings and work ongoing on this topic for typhoid conjugate vaccines.

However, I should be noted that typhoid vaccine trials have focused more closely on prevention of disease that on prevention of transmission of infection.

And we have quite limited data on vaccine impacts on fecal shedding of *Salmonella* Typhi.

Furthermore, modeling efforts by Ginny Pitzer's group and others suggest that elimination is unlikely through vaccination alone.

And that the role of chronic carriers as a reservoir for new infections represents a key epidemiologic uncertainty.

But we know from high-income settings that as typhoid incidence declines, chronic carriers play an increasingly prominent role as a reservoir of new infections.

Practical and accurate diagnostic tools to detect levels of infection that can lead to transmission

- **Typhoid clinical presentation not pathognomonic**
- **Diagnostics for disease**
  - **Blood culture sensitivity low, specificity high, and difficult to scale**
  - **Bone marrow culture more sensitive, impractical at scale**
  - **No solution yet**
- **Diagnostics for infection**
  - **Shedding without typhoid disease**
  - **Acute, convalescent, and chronic shedding with disease**
  - **Stool culture sensitivity low, specificity high, and likely impractical at scale**
  - **Vi serology for chronic carriage problematic in endemic areas and confounded by vaccine**

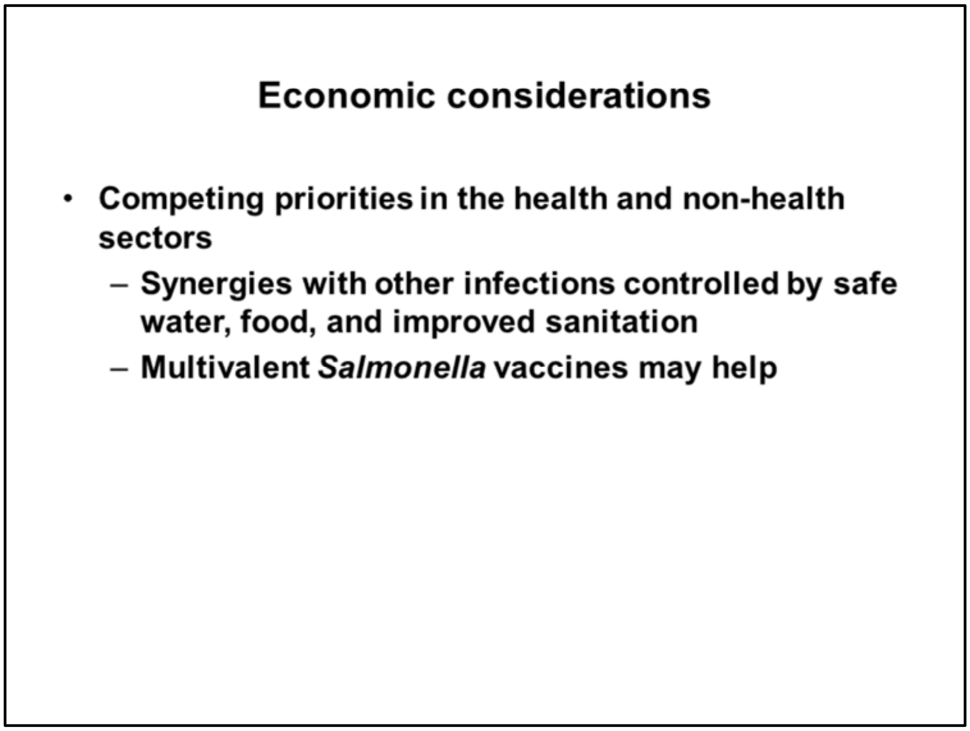
How about practical and accurate diagnostic tools to detect levels of infection that can lead to transmission?
I don't need to remind this audience that we face some challenges here.
Unlike smallpox and poliomyelitis where clinical presentation has a relatively narrow differential diagnosis, typhoid clinical presentation is far from pathognomonic.
Consequently we need to rely on widespread use of a diagnostic test to find cases.
As we know, blood culture's sensitivity is low, specificity is high, and it is a relatively difficult test to take to scale, a manifestation of limited investment in clinical microbiology services in low-resource areas.
Bone marrow culture is more sensitive, but often impractical locally let alone at scale.
And we have no major breakthrough yet for a test that is both practical and accurate for diagnosis of disease.
And if we face challenges with diagnosis of disease, there are greater challenges for the diagnosis of infection.
Salmonella Typhi may be shed in the absence of current disease.
And acute, convalescent, and chronic shedding may follow disease.
We know that a single stool culture lacks sensitivity for identifying shedding, and while specificity is high, repeat stool culture is likely impractical at scale.
We are aware that Vi serology may be a useful screening test for chronic carriage in low incidence settings, but the test has performed less well in endemic areas and may be confounded by vaccines that induce an anti-VI antibody response.
Shedding in the absence of disease and chronic carriage represents a potentially large and difficult to detect reservoir of bacteria, similar to that the silent reservoir that confounded historic schistosomiasis elimination efforts.

Humans the only reservoir

- **Reservoir: habitat in which agent normally lives, grows, and multiplies i.e., ‘amplification’**
- **Several lines of evidence are reassuring**
  - **Experience in Europe, North America, and elsewhere**
  - **Numerous old studies of finite environmental survival in many matrices**
- **Are we missing anything?**

Mitscherlich E, Marth EH. Microbial survival in the environment. Springer. 1984

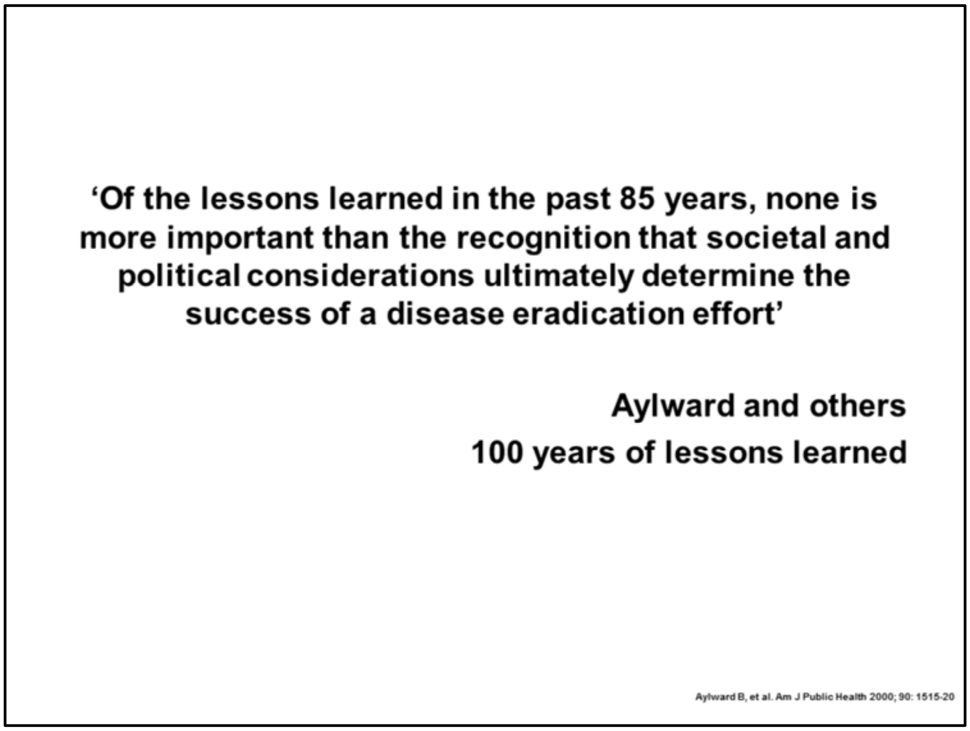
The final biological and technical factor is whether humans are the only reservoir of the pathogen.
Here I define reservoir as the habitat in which the agent, *Salmonella* Typhi in this case, normally lives, grows, and multiplies, often referred to as the site of ‘amplification’ of the pathogen.
Well, we have several lines of evidence that are reassuring here.
Including the experience of detailed epidemiologic investigations in Europe, North America, and elsewhere where human chronic carriers become the residual reservoir of autochthonous *Salmonella* Typhi transmission as typhoid incidence approaches zero.
And we have numerous, albeit quite old, studies documenting the finite environmental survival of *Salmonella* Typhi outside of the human host in many matrices, collated nicely in Mitscherlich (Mitch-er-lick) and Marth’s famous text.
However, I do think that it is important to ask ourselves if we are missing anything here.
Past experience reminds us, for example of the unexpected role of symbionts in cholera and dogs in dracunculiasis.



Economic considerations are numerous, but include competing priorities both within and outside the health sector.

For typhoid elimination, there are obvious synergies with other infections controlled by safe water, food, and improved sanitation.

But we are also conscious that *Salmonella* Typhi is only one of several *Salmonella* serovars that causes serious infections in humans and that multivalent vaccines with wider health impact could strengthen the case for investment.



Reflecting on efforts on disease elimination and eradication since 1915, the start of the first eradication effort targeting a human pathogen, yellow fever virus, Aylward and others said ‘Of the lessons learned in the past 85 years, none is more important than the recognition that societal and political considerations ultimately determine the success of a disease eradication effort.’

While biological and technical barriers, such as the discovery of the jungle cycle in the epidemiology of yellow fever virus transmission, contribute to failure, a lack of social and political support seems to be an enduring theme of unsuccessful efforts.

Social and political criteria

- Societal and political commitment from beginning to end and enormous cost of failure
- Buy-in from all levels of society and reasons for eradication
- Broad consensus on priority and justification
- Political commitment at highest levels
- Multi-level advocacy plan

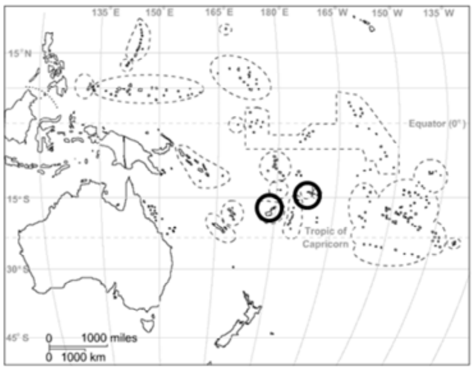
I won't go into detail on social and political criteria for disease elimination and eradication, but key points include that societal and political commitment is required from beginning to end and there is an enormous cost of failure both in economic terms, but also for future efforts.
Buy-in is required from all levels of society, including affected communities, and the reasons for elimination or eradication must be robust and accepted widely.
There needs to be a broad consensus on priority and justification.
And political commitment at highest levels, including at the level of national leaders and respected public figures who are willing to serve as champions.
Achieving these criteria requires a multi-level advocacy plan.

Social and political criteria

- **Technically feasible strategy identified, field-tested in a defined area, and found effective**
- **Complexities in implementation**
- **Sustainable improvement in health, high benefit to cost ratio**
- **Consequences for concurrent campaigns**

A technically feasible strategy must be identified, field-tested in a defined area, and found effective.
There are many complexities in implementation and agile programs that can respond to unexpected challenges are more likely to succeed.
The effort should lead to a sustainable improvement in health ideally also beyond the disease of primary focus, and ideally the program would have a high benefit to cost ratio.
And consequences for concurrent campaigns, both for disease elimination and other efforts, need to be considered.
The world is still working on unfinished tasks in eradication and elimination, including measles, poliomyelitis, and guinea worm to name a few.
I wanted to finish on the topic of identifying a technically feasible strategy, field-testing in a defined area, and demonstrating it be effective.

Islands of Oceania

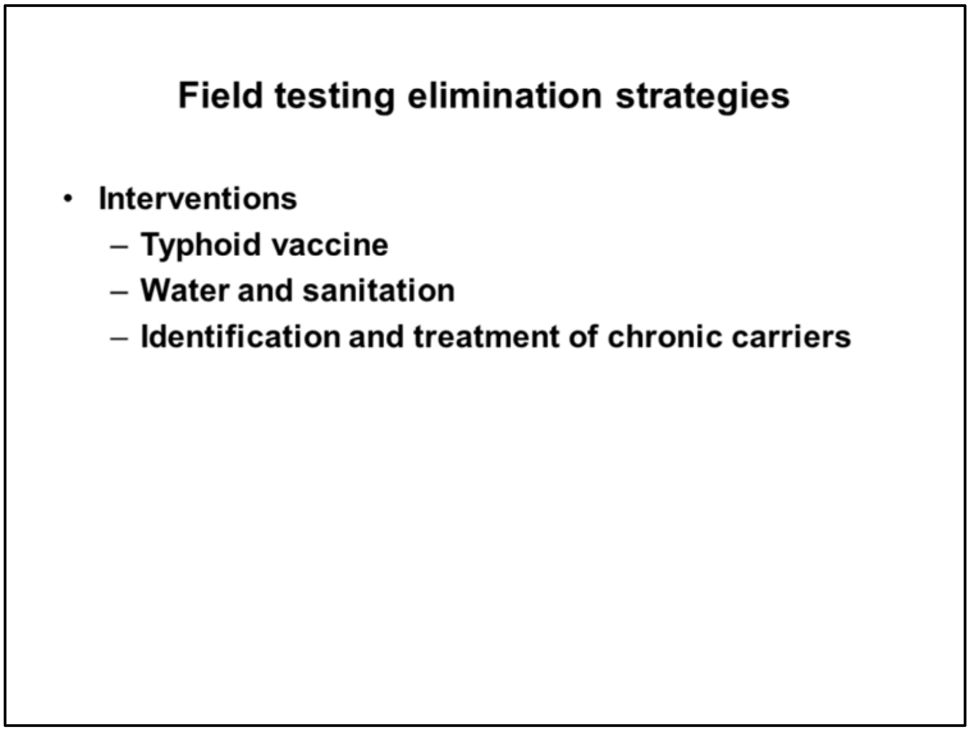


- **Leading efforts to control or eliminate endemic neglected tropical diseases: lymphatic filariasis, trachoma, yaws, soil-transmitted helminths, leprosy, scabies**
- **Fiji and Samoa both have major typhoid problems and social and political will**

Well, I might be biased but due to their small size and relative isolation, islands of Oceania have been leaders in efforts to control or eliminate a range of endemic neglected tropical diseases, including lymphatic filariasis, trachoma, yaws, soil-transmitted helminths, leprosy, and scabies.

Furthermore, the nations of Fiji and Samoa both have well documented and major typhoid problems with completed or ongoing basic epidemiologic research.

And both have substantial social and political will to control the disease.



And what elimination strategies would be field tested?
Well presumably interventions would include typhoid vaccine, improvements to water and sanitation, and if epidemiologically important, identification and treatment of chronic carriers of *Salmonella* Typhi.
Looking at this menu, the vaccine intervention might be the easiest and that water and sanitation intervention the most sobering.

HOW MAY TYPHOID FEVER BE ELIMINATED? *

A. ROBIN, M.D.

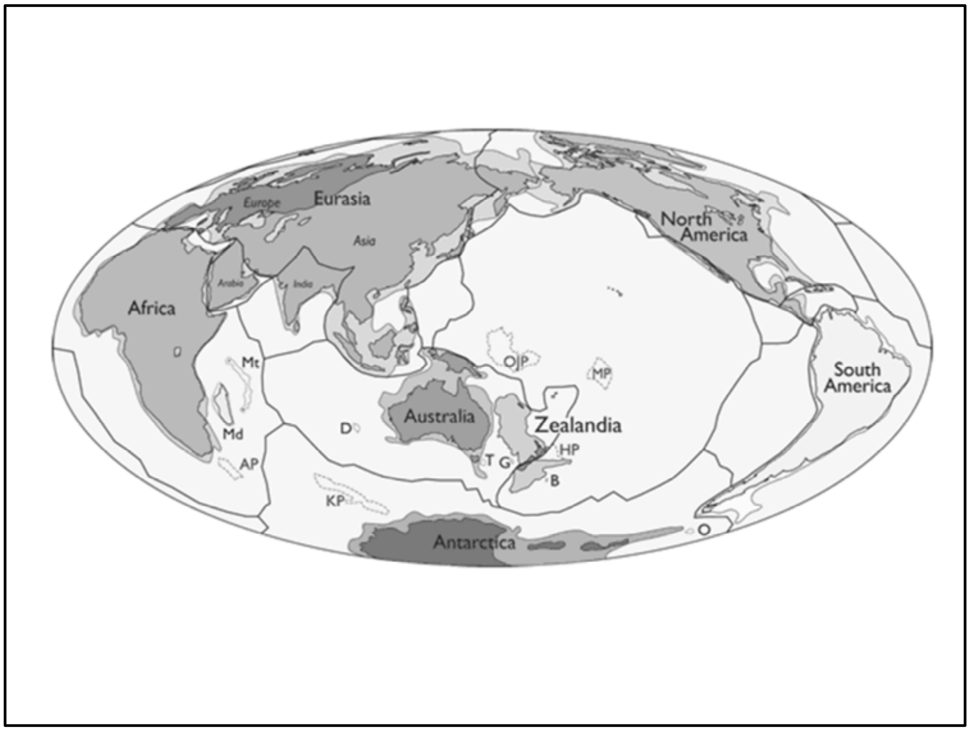
Bacteriologist to the City Water Department.

WILMINGTON, DEL.

The eradication of a given infectious disease requires an intimate knowledge of first, the causation or underlying etiologic factors, and second, the best methods of preventing these factors from operating.

Robin A. JAMA 1905; 44: 1082-88

Thank you for your attention.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