Modern Toolsets for Defeating Both Epidemic and Endemic Infectious Diseases

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Opinions expressed herein are those of the authors only
The Pathogens Responsible For Infectious Diseases are a Global Threat -- Their Actions Constitute an Ongoing Planetary Emergency of First Magnitude

- Most pathogens are Ancient Enemies of humanity -- often “at least as old as We are”
  - Have imposed titanic burdens of morbidity & mortality
    - Most all of our ~100,000,000,000 ancestors died of pathogenic diseases or malnutrition - not from the now-standard degenerative diseases of the Developed World
    - Have become ever-more-threatening as human population densities have soared, speeds & scales of transportation have climbed...
  - The 1918-20 ‘influenza’ pandemic killed ~10^8 people – well over 5% of all humans then alive
  - Before its global eradication in 1977 – culminating a WHO-sponsored campaign led by BA Henderson -- smallpox had killed ~100,000,000 people in the 20th century alone

- Overall burden
  - Over 11 M deaths every year from infectious diseases, nutritional disorders, and maternal mortality
  - Over 7 M of these annual avoidable deaths occur in children <5 years old

- Currently-endemic diseases
  - Malaria, TB and HIV
  - Pneumonia and other respiratory infections; enteric infections

- Pathogen eradication as a pathway to definitively addressing endemics – and obviating epidemics/pandemics
  - Resistance is always an issue for drugs and vector control: “Our wits against their genes!” -- Lederberg
  - Intense disease control - a novel ‘feature’ of modern times -- is vulnerable to reversals of funding, political failures and collapses of social order

- Zoonoses and other pathogenic sources of epidemics/pandemics of emerging infectious diseases, e.g.,
  - Ebola, Zika,...
  - Antigenically-novel and/or hypervirulent aeroviral strains: influenza, SARS/MERS,...

- Toolsets for Eradication end-game are useful for pandemic suppression as Eradication and pandemic control are dual problems
Global Disease Eradication Efforts

- Global Eradication of smallpox (*Variola major*) was a defining triumph of Our species
  - The *purposeful* extermination of a ruinous human pathogen

- Key lessons of the anti-smallpox campaign
  - Timely(!) case detection
  - Vaccination coverage and (eventual) logistics sufficiency
  - Adaptive tactics
  - Role of mid-Campaign technical- & programmatic innovations

- Rinderpest was the 2\textsuperscript{nd} Global Eradication triumph
  - Recapitulated lessons of the smallpox eradication campaign

- Early attempts against other diseases failed
  - Yellow fever
  - Malaria

- Other Eradication Campaigns are now nearing success
  - Polio
  - Guinea Worm

- New effort to Globally Eradicate malaria announced in 2007
Malaria Epidemiology and Burden has Changed Tremendously Since 2000

- Decrease in deaths from 839,000 in 2000 to 438,000 in 2015
  - Source: *WMR* 2015
- Scale up of LLINs, IRS, and ART
- Increase in financing
- Change in proportion of people living in different levels of malarial endemicity in Africa

The African Malaria Landscape Has Shifted

Vector Control Has Played A Major Role

- Just 2% of sub-Saharan African population slept under insecticide-treated net in 2000
  - ≥half of this population was ‘covered’ in 2015
  - Source: WMR 2015

- ITNs and IRS were responsible for much of the decline in endemicity, according to a recent analysis

Bhatt et al, Nature 2015
Enabled By Ever-Higher Levels of Funding
...But Progress Is Fragile

- Rise of pyrethroid resistance (and insecticide resistance more generally)
- Need to replace bednets frequently, maintaining high population coverage
- Shifts in vector species composition and feeding behaviors
  - Observed change in *An. farauti* biting behavior in Solomon Islands from 1972 to 2007
    - 1972 data from Taylor 1975
    - 2007 data courtesy Tanya Russell, MTC
  - Could make indoor targeting (nets and spraying) less effective
- Funding continuity and social order issues
  - Recent example of Venezuela
Malaria Eradication Is A Big, Long-Term Goal

- Global Malaria Eradication was attempted before (~'58 - ~'70)
  - It is not easy to complete

- A renewed effort was launched at the Malaria Forum in 2007

- Ideal: the burden of malaria is stably at zero forever, robust to any kind of reversal
  - Pesticide and drug resistance, economic crisis, fatigue, etc...
  - Given numbers, time, and pressure, Evolution – “..their genes” -- will win otherwise

- Malaria Eradication is difficult

- Extensive heterogeneities
  - Baseline transmission intensity
  - Multiple local vector species
  - Population densities
  - Types of housing
  - Baseline health care
  - Resistance statuses
  - Immune status

- Many logistic-challenging areas
Basic Analytical Framework for Eradication

- Partition into regional elimination efforts and prioritize
- Reduce transmission
  - Vector control
  - Prophylaxis
  - Vaccines?
- Clear infections
  - Diagnostics
  - Drugs
  - Campaigns
- Prevent reintroduction
  - Case management
  - Surveillance
  - Aided by “stickiness”? (DL Smith)

- Available tools (present + 10 yrs)
  - Drugs
  - Single-encounter, radical-cure
  - Prophylaxis
  - Diagnostics
  - Vaccines?
  - Vector control
    - Nets
    - IRS
    - Larval control, source management
    - New approaches (e.g., genetic gambits)
  - Field logistics support
    - Polio example
  - Modeling and quantitative analysis
  - Data systems and monitoring
Data Analysis and Mathematical Models Aid Understanding of Local Epidemiology

2013 Round-1 Household Prevalence
Gwembe, Southern, Zambia
Malaria Seasonality in Zambia

Hot Dry Season

ZAMBIA
Gwembe District

RDT-confirmed clinical cases


Dec 2012

Lakefront
Using Malaria Genomics to Detect Changes in Transmission in Senegal

A

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Daniels et al. *PNAS* 2015
What Does it Take to Complete the Global Eradication of Wild Poliovirus?

- Progress over past two years — compared to a 12-month window from June 2014
- Need to clear last pockets-of-contagion in Nigeria, Pakistan, and Afghanistan

Wild Poliovirus Cases¹, Previous 12 Months*

*11 June 2013 – 10 June 2014

*Excludes cases caused by vaccine-derived polioviruses and viruses detected from environmental surveillance.

Data is WHO HQ as of 10 June 2014
Figure 5 Model predictions from the selected model for June through November 2013. (A), The predicted risk, or expected number of cases, under the model. (B), The predicted probability of one or more reported cases, i.e., the output from the binomial portion of the hurdle model. (C), The predicted number of reported AFP cases given an introduction (one reported AFP case). All estimates based on covariates from December 2012 through May 2013.

Upfill-Brown et al., BMC Medicine 2014
More Was Needed for Polio in Nigeria

- Better Population Maps
  - Remote sensing and feature extraction to map where people live
  - Development of new microplans

- Vaccinator Tracking
  - Super-resolution photogrammetry- and GPS-enabled
  - Real-time coverage estimation
  - Targeting of un-reached neighborhoods, even houses

- Investment in Cold Chain technologies
  - Storage
  - Outreach
  - Situational awareness

- Access and security for vaccinators
Vaccinator Tracking with Improved Population Maps Allows Real-time Coverage Estimates
Polio Investments Helped Interrupt Ebola in Nigeria!
But We are Not Ready for Next Epidemic
Innovation is Needed for Endemic Disease Eradication and Suppression of Pandemics

- Areas for Innovation
  - Innovation in Vaccine Cold Chain support
  - Innovation in Vaccines
  - Innovation in Drugs and Drug Delivery
  - Innovation in Novel Vector Control
  - Innovation in Immunological Tools

- Delivery and Logistics are key!
  - Innovation that facilitates this are very desirable
  - Information systems

- International enabling environment
  - Rapid, extensively-rehearsed set-of-responses
  - Pre-authorization and funding-in-the-bank
Innovation in Vaccine Cold Chain Support

- New cost-efficient vaccine refrigerators for challenging (e.g., low-quality power) conditions
  - E.g., MetaFridge

- New-technology vaccine outreach support
  - Evaporates cold water/ice at low pressure to provide shelf-stable, weight-efficient thermal battery
  - Aimed to supplant present ice-filled carriers
Unprecedented Logistics Support Enabled Via ‘Boiling Ice’

Device initially turned on (Charged in Seattle)

Ambient temperature measured on outside of carrier. Variations caused by movement of device, exposure to sun etc.

Lid openings of device, vaccinator retrieving vaccines from unit.

Day 1  Day 2  Day 3  Day 4  Day 5

Performance of PortEvap during May IPD campaign in Kano
Innovation in Drugs

- Gastric retention devices that release drugs over days to weeks after single-occasion oral ingestion
- Extend pharmacokinetics far beyond traditional time constants
- Improves ease of delivery, achievable coverage and adherence, and duration of biomedical action
- Bob Langer and Gio Traverso at MIT have demonstrated working prototypes for ivermectin
Innovation in Vaccines

- Timed-release packaging for immunogens
- Receive entire course of a timed pulsatile-release vaccination series in a single injection
  - Technology demonstrated for IPV by Bob Langer and Ana Jaklenec at MIT
  - Also supports single injection administration of previously-incompatible vaccines
- Now firmly on the path to comprehensive and enduring immunization at birth
  - Reliable protection against all vaccination-preventable pathogenic diseases

Pulsatile Release Kinetics
Innovation in Modified Mosquitoes—Gene Drive for Individual Anopheles Species

Available drive techniques

Effect of germline homing

8 Years After Release
Population Eliminated
Construct At Fixation
Mix of Wildtype and Gene Drive
Loss of Construct

Burt, Phil Trans Roy Soc B 2014
Eckhoff et al, under review
Innovation in Immunological Tools

**Required Processes**

**Surveillance for Novel Pathogen Strains**
- Incentives-based
- Clinical samples
- Travelers at choke points
- Random sampling in key areas

**Rapid Sequencing**
- Provide situational awareness of strain distributions
- Identification of Novel strains
- Identification of Potent strains

**Identification of Best Responders**
- Test for antibody affinity to strains of interest
- Harvest mAb and cells for future use

**Parallel Tracks For Implementation**

**Harvest mAb; fractionate, purify, package**

**Distribute to local folks for therapy and prophylaxis (100X)**

**Retain best responders; pay for continued harvesting**

**Seed mAb production with highest-affinity mat'ls**

**Storage and broad geographic fan-out, both real-time responsively and Model pre-planned**

**Treatment of population to keep pathogen from escaping, keep pathogen from entering, or to suppress outbreaks**
The Pathway Forward

- Infectious Diseases are a **Major Planetary Emergency**
  - The ongoing annual death toll is notably severe
    - We've recently seen ≤10% of the human race pathogen-slaughtered in 2 years
  - Pandemic risks from emerging pathogens threaten everyone, everywhere, *continually*
    - Ebola in Houston & Lagos; Zika in Miami & New York; SARS in Beijing & Toronto
    - Especially 'if anything really goes wrong' in a major population-pool

- Innovation — guided by scientific study, computation, and strategy — is urgently needed to inform enhance actions
  - Extant means are dubiously sufficient — and are being continually ‘outgrown,’ as well as over-matched

- International partnerships — with established, pre-staffed/equipped/exercised, pre-funded response capacities — are core components of what are required

- The same capabilities can be exercised to complete disease regional elimination and Eradication efforts — while keeping these fully prepared to address hyper-epidemics