Plan to Combat the PRPC

Two-Pronged Approach for 2055 Emergency

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Background

Cause of the Pan-Resistant Pathogen Crisis (PRPC)

A wide range of bacteria have acquired resistance to multiple antibiotics.

Bacteria reproduce very quickly. Mutations arise, and if they are beneficial, can be passed down, causing rapid evolution and adaptation to new environmental conditions.

The inappropriate use of antibiotics and antimicrobials in medicine and in agriculture create a selective environmental pressure that favors resistant bacteria.

Bacteria are able to transfer portions of their genes to other bacteria through horizontal gene transfer.

Under these conditions, pathogens with drug resistance are more likely to survive and reproduce and can transfer their resistance genes to new bacteria.

Notable Symptoms

Respiratory Infections

- Breathing difficulties
- Chest pain
- Persistent coughing
- Respiratory failure

Urinary Tract Infections

- Severe discomfort
- Fever
- Frequent urination
- Renal damage
- Sepsis

Gastrointestinal Tract Infections

- Severe diarrhea
- Cramping in the abdomen
- Dehydration
- Colitis

Skin/Soft Tissue Infections

- Painful boils
- Abscesses
- Spread of infection to bones and organs
- Sepsis

Demographics

- While PRPC is dangerous to all humans due to its very nature and the difficulty of treating it, certain populations are at greater risk.

- Small children
  - Quick disease progression
  - Lifelong consequences of infection
- Elderly
  - More severe symptoms
  - Greater death rates
- Low-income and marginalized communities
  - Low immunization rates
  - Lack of access to healthcare
  - Increased exposure to unhygienic environments

- Less-developed countries
  - Inadequate healthcare systems
  - Limited access to new treatments and drugs
  - Greater prevalence of treatment-resistant illnesses
- Urban vs. Rural Areas
  - Disease spreads more quickly in urban areas
  - Rural areas struggle with lack of medical infrastructure and staff

Evasive Mechanisms

Bacteria have sophisticated mechanisms that evade the effects of antibiotics

Efflux Pumps	• Are transport proteins in bacterial membrane that eject things from cell • Can expel a wide range of toxic substances, such as antibacterial compounds • Are involved in biofilm formation and in extruding factors that make the bacteria more virulent
Beta-lactamases	• Destroy an integral structure of Beta-Lactams, the most widely used and effective antibiotics • Briefly circumvented by combination therapy of Beta-lactamase inhibitors plus antibiotic • Combination therapy rendered ineffective by new bacterial evolution
Target Sites	• Play a vital role in microbial life and are used for selective antimicrobial action • Spontaneously mutate, reducing their susceptibility to antibiotics • Genetic changes to target sites can be transferred to new organisms via genetic exchange
Biofilm Shields	• Are thin layers of microbial communities adhered together and enclosed by secreted substances • Delays antimicrobial penetration into cells • Creates conditions inside where bacteria are less metabolically active and more resistant

02

Two-Pronged Approach

PREVENTION

A top down approach in the modern era

Global Effort of Prevention

From the international to local level, everyone has a role to play.

The WHO

- Rapid early response and assessment of outbreaks
- Compile international statistics into actionable data
- Establishing norms and standards
- Convening the global community to set goals
- Mobilize resources

Countries

- Surveil for notable outbreaks and track resistant gene spread
- Promote prevention campaigns nationally
- Prevent inappropriate use of antibiotics in humans, animals, and agriculture
- Implement latest sanitation systems

Local Governments

- Utilize intimate knowledge of their communities to create best-fit policies
- Build trust with the public
- Operationalizing national prevention guidelines
- Create committees of qualified and trusted locals to guide community action

Utilizing Social Media

In the modern era, public sentiment toward global events is shaped not only by conventional news sources, but by the collective opinions that are formed through social media.

If there is to be any hope of public unity toward prevention efforts, efforts must be made to garner support online.

- Potential methods include:
  - Sponsoring influencers to read ads, in this case, messages promoting prevention
  - Encouraging the use of hashtag trends that promote prevention efforts
  - Sponsoring educational content creators to make videos on PRPC and ways to prevent the spread

RESEARCH INNOVATION

Addressing a Root Cause

A Multiplicity of Mechanisms

- There are many potential avenues of research to pursue
- Each bacterial evasive mechanism should be researched to find methods of counteracting them, for example:
  - Natural, nontoxic EPIs (Efflux pump inhibitors)
  - Novel BLIs (Beta-lactamase inhibitors) to counter bacterial ability to combat our most widely used antibiotics
  - And more ARBs (Antibiotic resistance breakers)

While research must continue on ARBs, there is pressure to focus our global efforts on a specific research direction that could address the root cause of rapid resistance evolution.

Focusing Our Efforts

There are a multitude of mechanisms that bacteria use to become resistant. In this time of crisis, there is not enough time to pursue counters to each mechanism.

- How do bacteria so rapidly spread new mutations throughout their populations?
  - Rapid generation times
  - Selective environmental pressures
  - Horizontal gene transfer

  The quick reproductive life cycles of bacteria are difficult to slow down.

  We must continue our attempts to treat bacterial diseases, so the environmental pressure of antibiotics will continue to select for resistant bacteria.

Horizontal Gene Transfer (HGT)

- The process by which DNA is transferred from one cell to another
- HGT allows plays a major role in the acquisition, accumulation, and dissemination of antimicrobial resistance genes
- One way bacteria transfer DNA is through conjugation
    - Contact-dependent; a donor attaches via a mating apparatus to a recipient and passes DNA
    - Antimicrobial resistant genes are often found on the shared DNA
- Conjugation has been identified as the most important process for the dissemination of antibiotic resistant genes in bacteria
- There is evidence that the rate of conjugation increases in the presence of antimicrobials

By finding a way to prevent or slow the rate of conjugation between bacteria, the overall rate of resistant bacteria development may be slowed, giving researchers more time to develop new mechanisms to combat the PRPC.

Nanomedicine

- Incredible recent developments in bioengineering allow the crafting of nanoparticles
  - Can be intentionally created with unique properties tailored to specific use
- Advantages of using nanoparticles
  - Targeted delivery and controlled release
  - Small particle size facilitates entry into target cells
  - Reach desired sites without affecting neighboring healthy tissue
- Research direction for combating PRPC
  - Design nanoparticles capable of targeting conjugation structures in bacteria
  - Impede or destroy bacterial ability to transfer resistant DNA between themselves

Once a targeted nanoparticle is created, it is time for clinical trials to test its ability to interfere with conjugation in actual bacterial populations.

Clinical Trials

Hypothesis: Damaging or destroying bacterial ability to conjugate will slow the rate at which antimicrobial resistance genes spread through a population of bacteria.

The goal is to create a nanoparticle that would successfully and consistently reduce the rate at which the antibiotic resistant genes are spread throughout the population.

Stages of the Trials

Determine the ratio of antibiotic resistant to non-resistant bacteria within one population.

- Cultures in Agar Plates
  - Take a sample from the known population and divide it between two plates, neither with antibiotics applied to them.
  - Apply nanoparticle to one of the plates.
  - Observe the ratio of resistant to non-resistant bacteria after several generations for both plates
- Test cultured plates with and without antibiotics applied to them
  - The presence of antibiotics has been shown to increase rate of conjugation, so the nanoparticle must be able to interfere significantly with conjugation under more difficult conditions

Stages of the Trials (Cont'd)

- Further stages of testing should involve a combination of Microphysiological Systems (MPS) testing and *in vivo* testing in rats
- MPS:
  - An *in vitro* method often referred to as an "organ-on-a-chip," enables the study of normal organ function and effects on organ function using human cells
    - Conduct trials similar in structure to that with bacterial culture agar plates
    - Introduce a known population of bacteria to each MPS chip
    - Apply nanoparticle to one of the chips
    - Observe ratio of resistant to non-resistant bacteria in future generations
  - The benefit of MPS is to observe whether the introduction of the nanoparticle results in a better outcome for the cells/tissues/organ systems modelled by the chip

Stages of the Trials (Cont'd)

- *In vivo* trials in rats
  - Questions to be answered:
    - Is the nanoparticle is effective *in vivo?*
    - Does the nanoparticle have any unexpected effects on non-target organ systems?
    - Are antibiotic treatments more effective when combined with the nanoparticle treatment?
  - As in previous trial stages, determine if introduction of the nanoparticle produces a lower ratio of resistant to non-resistant bacteria compared to the control after several bacterial generations
  - Perform trials where both rats are treated with antibiotics and observe whether the antibiotic treatment is more effective in rats with the nanoparticle

Human Trials

Initial Small Clinical Trials

- Does the nanoparticle:
  - Reduce conjugation between bacteria
  - Lower ratio of resistant vs non-resistant bacteria after several generations
  - Improve individual's response to antibiotic treatment
- Are there unexpected side effects or evidence that the nanoparticle targets systems it is not supposed to?

Further Large-Scale Trials

- Once small trials repeatedly prove safe and effective, large-scale trials should commence with haste due to magnitude of crisis
- International cooperation should facilitate trials in different corners of the world
- Test if nanoparticle treatment proves effective for:
  - Immunocompromised individuals
  - Children
  - Elderly

Technical Challenges

- Difficulty tailoring nanoparticle to target conjugation mechanisms
- Infiltrating biofilm shield
  - Small nanoparticle size improves chances of overcoming biofilm barrier
- Outpacing continued bacterial evolution
  - Nanoparticle must have a structure that can be easily modified in the case of further bacterial mutation
- Time constraints under crisis conditions
- Organizing large-scale trials internationally

03

Considerations

Public Response

How to manage public mistrust and fear:

- International
  - Demonstrate the goals of the WHO and the need for unity through social media messaging and interaction
  - Strong communication of successes internationally
- National
  - Collaboration with state and local governments to put together visible and effective prevention campaigns
  - Use social media to celebrate successful delivery of supplies and personnel to hospitals
  - Monitor rumors and misinformation, providing prompt responses and factual information
- Local
  - Provide avenues for community members to voice their concerns to local officials
  - Maintain regular communication through news conferences on mayoral and gubernatorial levels

Costs

A key component of the success of the two-pronged solution is for the international community to buy-in on pooling funds for both prevention and research.

- The WHO should
  - Have a dedicated budget for research and clinical trials, and UN nations should work together to provide additional funds as necessary as trials progress
  - Provide guidelines and advice for federal, state, and local government prevention budgets
- The IMF
  - Can create a PRPC Trust that UN nations contribute to
- Blended finance
  - Blends public and private capital to attract private investment in combating PRPC

Concerns

Is it best to focus research on preventing continued evolution rather than developing more rigorous treatments for the currently afflicted?

- The goal of the dual-pronged approach is to address both the present and future of this crisis
  - Prevention
    - Encourages international, national, and local levels of government to work together with local communities to address the immediate crisis
    - Budgets set aside for the crisis should fund necessary resources to treat illnesses at the highest available quality
    - The goal of international cooperation should be to distribute high quality medical supplies and prevention materials to all nations
  - Research
    - Addresses the root cause of the crisis: unbridled bacterial evolution
    - Aims to prevent the crisis from worsening further and slow its development

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