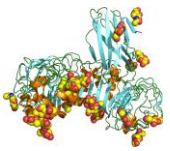



The Post-Antibiotic Era and a New Focus on Immune Health

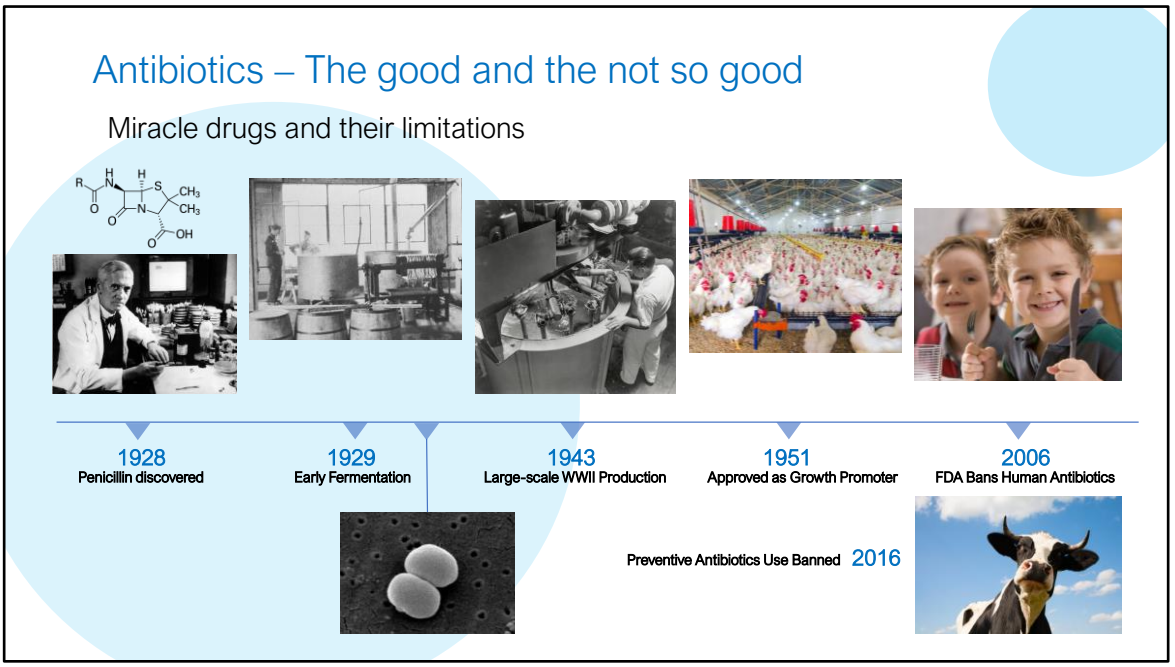
An issues-oriented webinar for the conscientious investor

April 2020

www.zivobioscience.com

Hello and welcome to this series on life science investing. Today we explore the role of antibiotics in the 21st century and its effect on everything from the environment to food safety, followed by research trends and market intelligence regarding immune health.

This webinar is presented by Dr. Amy Steffek and Bill Pfund, senior research & development principals at ZIVO Bioscience, Inc. a US-based biotech company



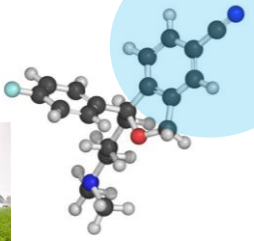
When penicillin and antibiotics in general were first discovered, they seemed almost miraculous, fighting infectious diseases and allowing wounds to heal quickly. By 1951, antibiotics were approved as growth promoters in poultry, swine and beef cattle, in other words, pre-emptive use. But by 2006, there was compelling evidence that drug resistant bacteria and unmetabolized antibiotics where finding their way to the dinner table. When might you think drug resistant bacteria were first observed? That would be 1932…

….just two years after penicillin was made available in very limited quantities. We're all aware of drug-resistant bacteria, some of which are deadly, such as tuberculosis and MRSA. Much of this has to do with overuse of antibiotics for common infections, but a significant number of infectious pathogens emanate from animal products. And not something very exotic. Your everyday supermarket chicken should be prepared and cooked with diligent care.

In addition to drug-resistant bacteria is the presence of unmetabolized antibiotics in animal products – drugs fed to the animals that weren't fully used up and remain in the flesh or the milk. These unmetabolized drugs are in fact dosing our children with active pharmaceuticals, potentially leaving physicians with fewer options to treat infectious disease in their future. In 2016, the US FDA finally banned the preventive or pre-emptive use of antibiotics in dairy cows because unmetabolized drugs where showing up in the milk supply.

Antibiotics – The good and the not so good

Drug pollution of water and irrigated farmlands

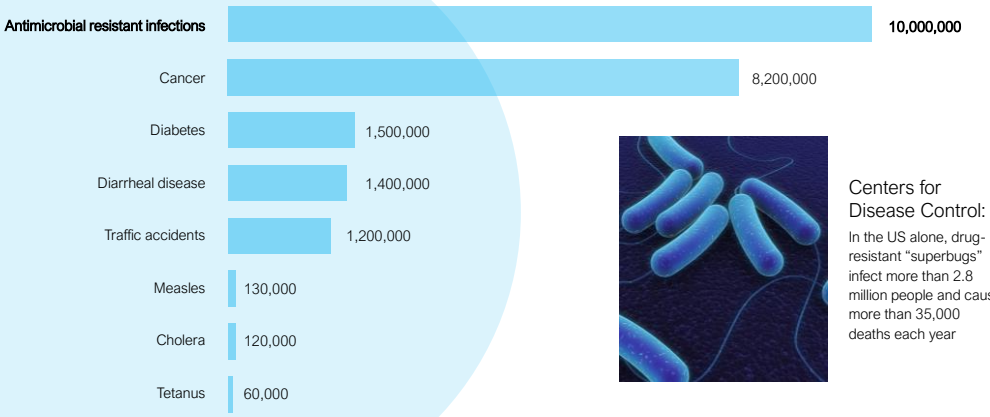


We can go further down this line of inquiry. There is no municipal sewage treatment plant in the world that can remove unmetabolized over-the-counter or prescription drugs from the water released back into the environment. So, the water may be technically safe to drink, but it may well contain traces of antibiotics, antidepressants and steroids not fully metabolized by our bodies and eliminated into a sewage treatment system not designed to process these compounds. Many of our lakes, rivers and oceans are tainted with biologically active therapeutics. That same water is drawn for irrigation, repeatedly soaking the food crops we eat.

Antibiotics – The good and the not so good

Deaths from Drug-Resistant Infections in 2050

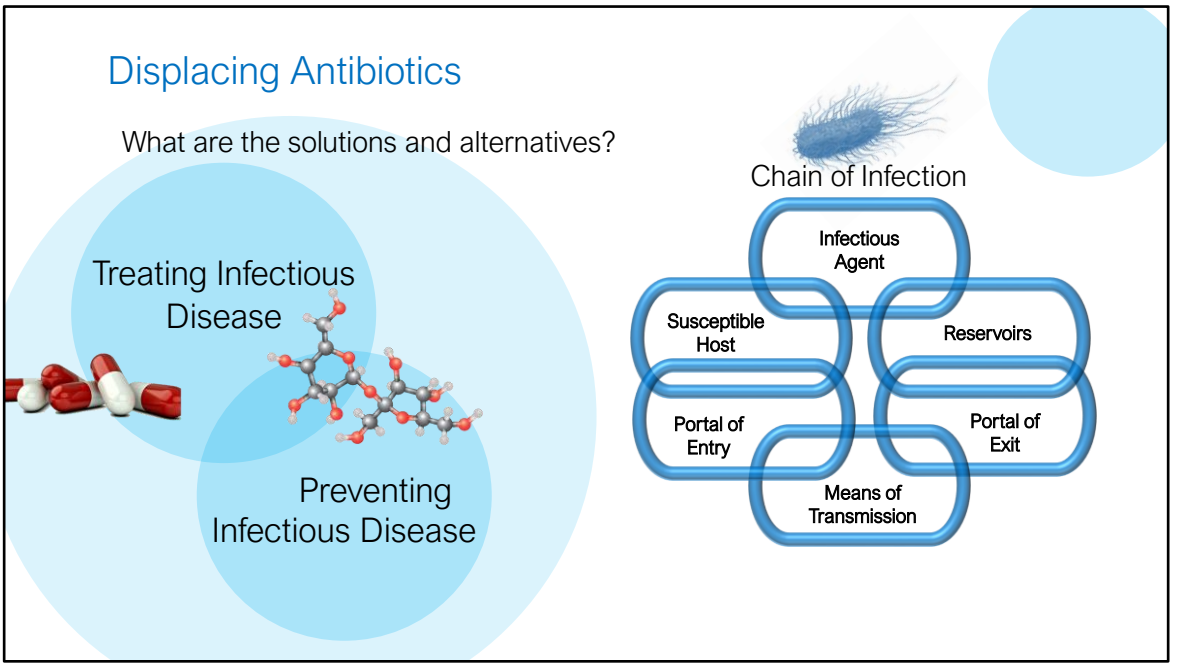
Source: Review on Antimicrobial Resistance 2014



Centers for Disease Control:

In the US alone, drug-resistant "superbugs" infect more than 2.8 million people and cause more than 35,000 deaths each year

Certainly, we can't continue down this path as this chart suggests. Non-antibiotic alternatives for pre-emptive use and growth-promotion are needed to slow down drug-resistant bugs.

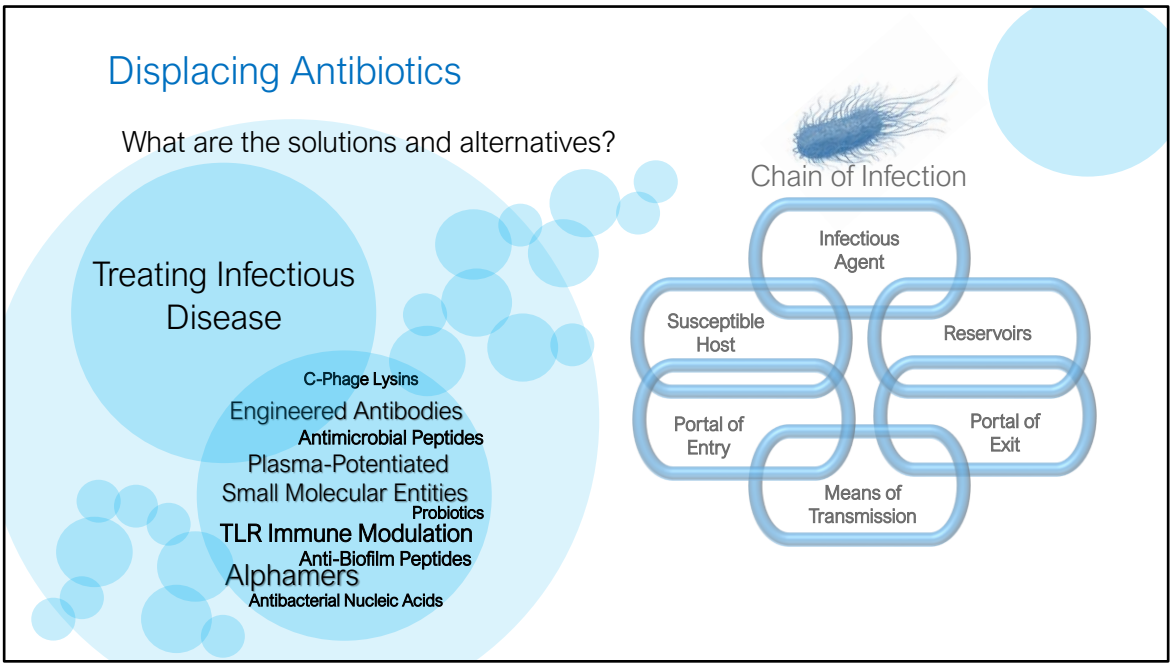


Antibiotics will continue to have a place in medicine for the foreseeable future. But the pharmaceutical industry is acutely aware that it is in a race with drug-resistant pathogens to treat infectious diseases. And, it's the peripheral or pre-emptive use of antibiotics that is helping to fan the flames. In general, there are two strategies being applied to displace the use of traditional antibiotics:

#1. Treating infectious disease by means other than the use of antibiotics

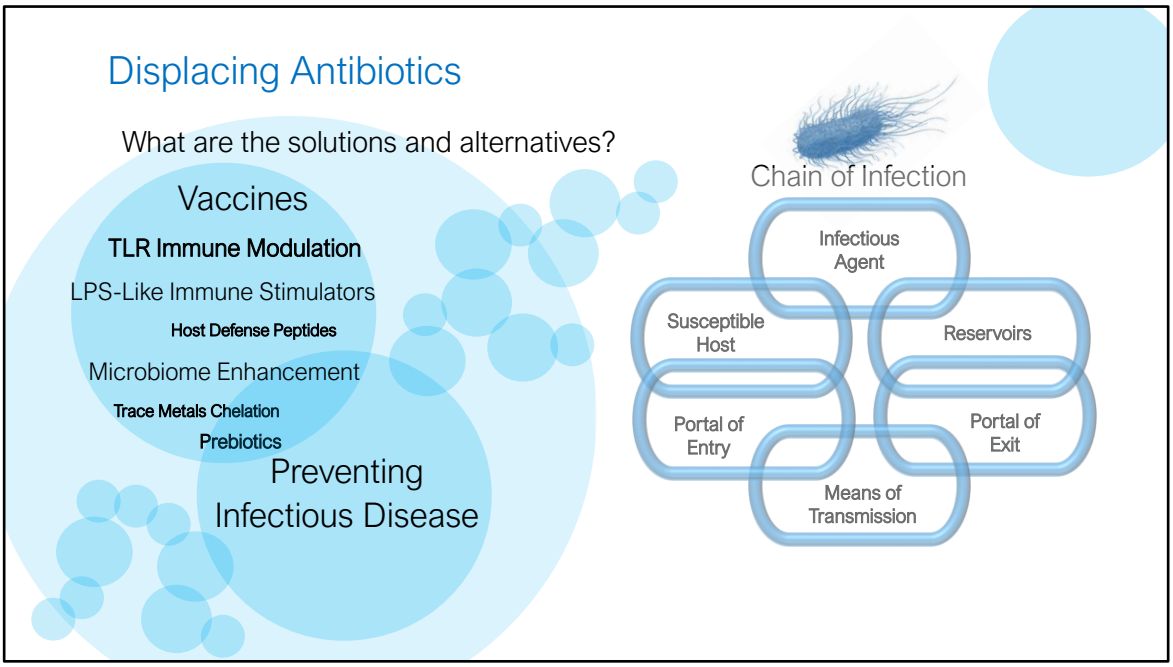
#2. preventing infections before they occur using non-antibiotic alternatives

In both cases, scientists are trying to break the chain of infection, and any link in the chain is fair game. In the last century, most of the focus has been on targeting the infectious agents themselves and to some extent interrupting the means of transmission



According to a recent paper in the British medical journal Lancet, traditional antibiotics and antimicrobials are still the mainstay in fighting infectious diseases in humans and animals. But the authors identify promising research and some early successes with alternative treatments, such as C-Phage lysins – enzymes that partially digest invading bacteria, as well as other approaches directly targeting the invading pathogen.

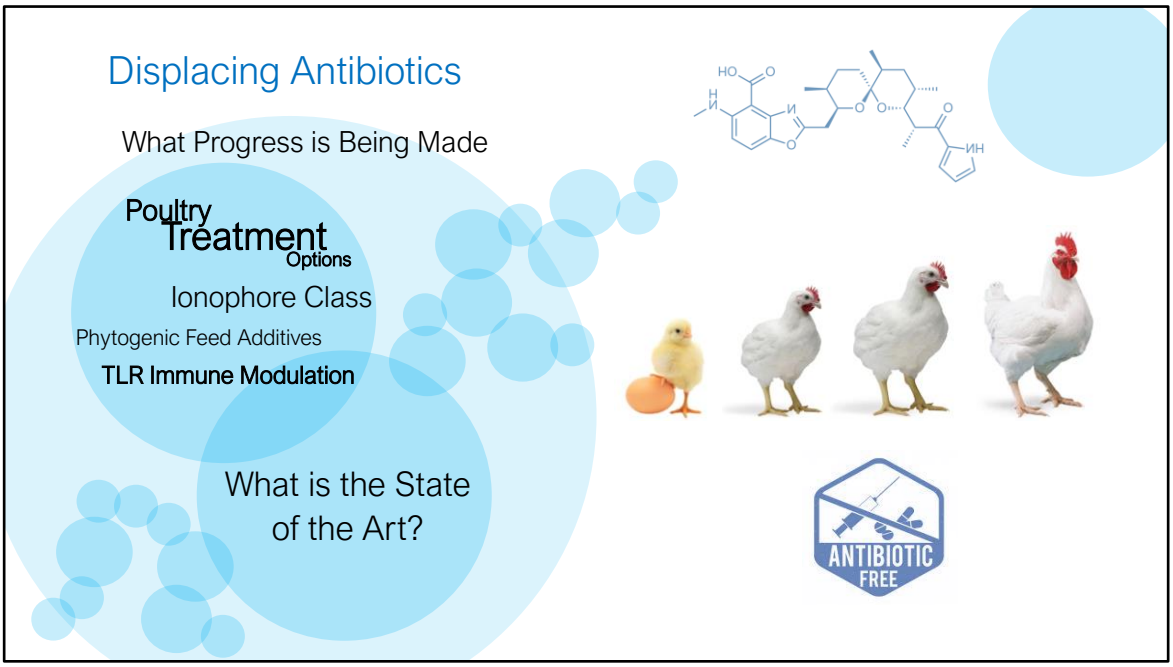
There is also significant effort being focused on augmenting the immune response, by injecting engineered antibodies or antimicrobial peptides, for example, or stimulating the immune system by other means. Although a few compounds using this approach are in clinical trials, many are years away from market entry.



In terms of preventing disease, vaccines represent the most common and familiar option. However, each vaccine usually targets only a single pathogen and there are hundreds of them.

Probiotics and prebiotics stimulate the immune system, help build a healthy microbiome, or offer the building blocks to create a more robust immune response to some degree, but I'd like to draw your attention to TLR Immune Modulation.

TLR stands for toll-like receptor. Suffice it to say, that much of the current research is focused on using our own immune system to fight and prevent disease, rather than targeting the infectious agent directly. So, in the chain of infection, this would help make the host less "susceptible" and break the cycle

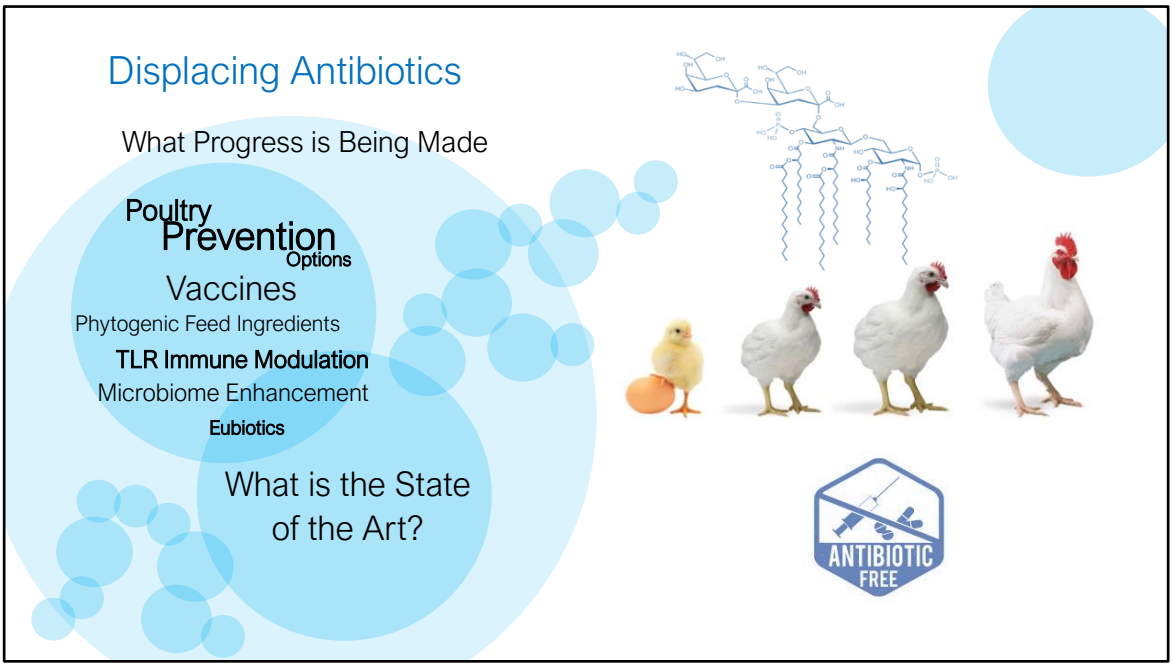


The poultry industry, where prophylactic use of antibiotics was once the norm, is a good example of where we currently stand in the overall effort to displace antibiotics

On the treatment side, the most commonly used drugs are the ionophores -- a special class of antibiotics not used in human medicine. But they have one glaring drawback: They lose effectiveness after a couple of weeks. Poultry producers must therefore continuously rotate ionophore treatment programs to stay ahead of infective pathogens. And, they still hold the potential to create resistant pathogens.

On another front, phytogenic or plant-based feed additives as a treatment for poultry pathogens are getting some attention from poultry producers, but the science behind them is lacking and results are mixed

Finally, immune modulators, specifically TLR modulators, are in the development pipeline because some may be effective treatments for common poultry infections. This is an area of research where ZIVO is deeply involved. For example, ZIVO's lead immune modulator for poultry has been tested in more that 15 clinical studies to prove its effectiveness and to define its mechanism of action.



From the prevention perspective, poultry vaccines are widely used, but they lack overall effectiveness. Vaccines for coccidiosis, for example, a parasitic infection of the intestinal tract, are generally believed to be only 40% effective and chemical treatments such as ionophores are often used in parallel in an attempt to offer the same level of protection as antibiotics

A growing number of plant-derived “phytochemical” or “phytogenic” ingredients are being marketed as “natural” alternatives to antibiotics and ionophores, but again, the science isn’t there yet in terms of efficacy, while high prices and availability affect widespread adoption

Finally, eubiotics, defined as the promotion of beneficial gut microbes in the intestinal tract, represents another very hot area for product development. This category includes oligosaccharide pre-biotics, fragments of beneficial microbes, and live probiotic bacteria added to feed. Some of these products, such as ZIVO’s Immunoalexin ingredient, are poised to enter the market in the near future.

Market Intelligence

Strong, Growing Demand Across the Globe

Poultry Market Annualized

Vaccines -	$2.0B	6.2% CAGR
Phytogenics -	$800.0M	9.8% CAGR
Eubiotics -	$1.6B	8.3% CAGR
Coccidiostats	$1.5B	3.2% CAGR**

**Primarily Ionophores

The ability to grab market share with a truly effective antibiotic alternative is possible, especially given the lackluster effectiveness of currently available alternatives.

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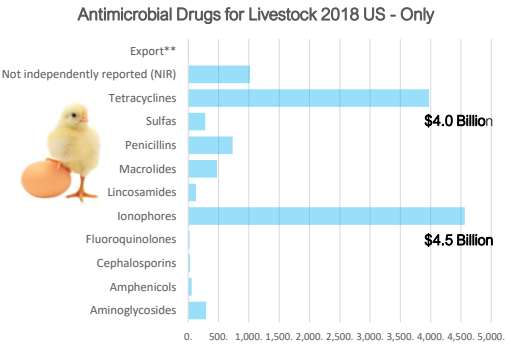


The ability to grab market share with a truly effective antibiotic alternative is possible, especially given the lackluster effectiveness of currently available alternatives.

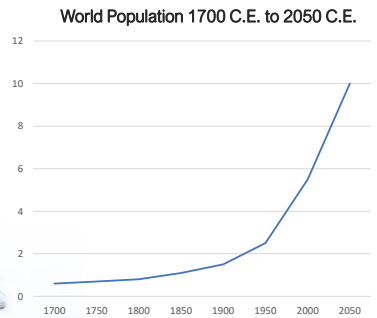
Please note US sales of ionophores for livestock, which includes poultry shown here on the right -- $4.5 billion annually. And, please note that tetracyclines, which are antibiotics, still enjoy sales of $4 billion annually in the US despite intense consumer and regulatory pressure. As a result, the market for antibiotic alternatives, especially natural product alternatives, is simply massive.

Market Intelligence

Strong, Growing Demand Across the Globe

Human Market Annualized

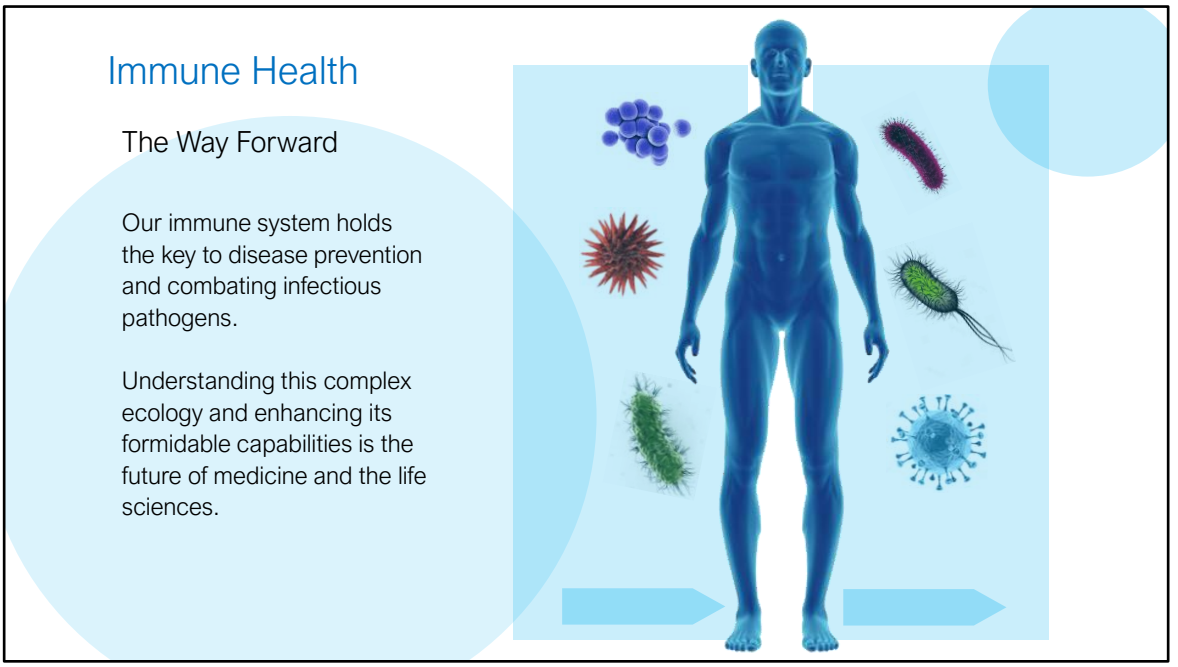
Antibiotics	$40.0B
Probiotics	$56.6B
Autoimmune	$110.0B
Antidiabetic	$78.7B



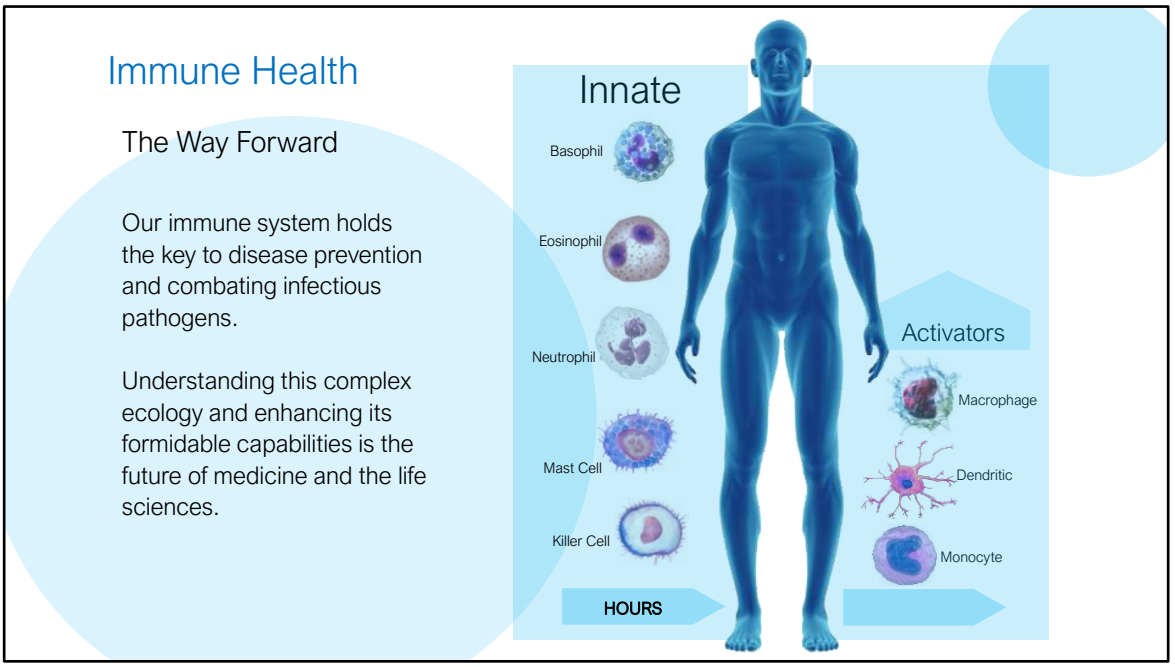
The world's human population is expected to exceed 8 billion in a few short years, and especially given recent current events, we all very well know there is no shortage of infectious diseases or immune disorders. As a result, billion-dollar markets for antibiotics, autoimmune disorders and diabetes will continue to grow.

What's interesting is the $56 billion spent on probiotics worldwide in 2019. This indicates an awareness and an appetite for non-drug alternatives to getting healthy and staying that way.

Probiotics and prebiotics are the gateway to gut health and ultimately, to immune health

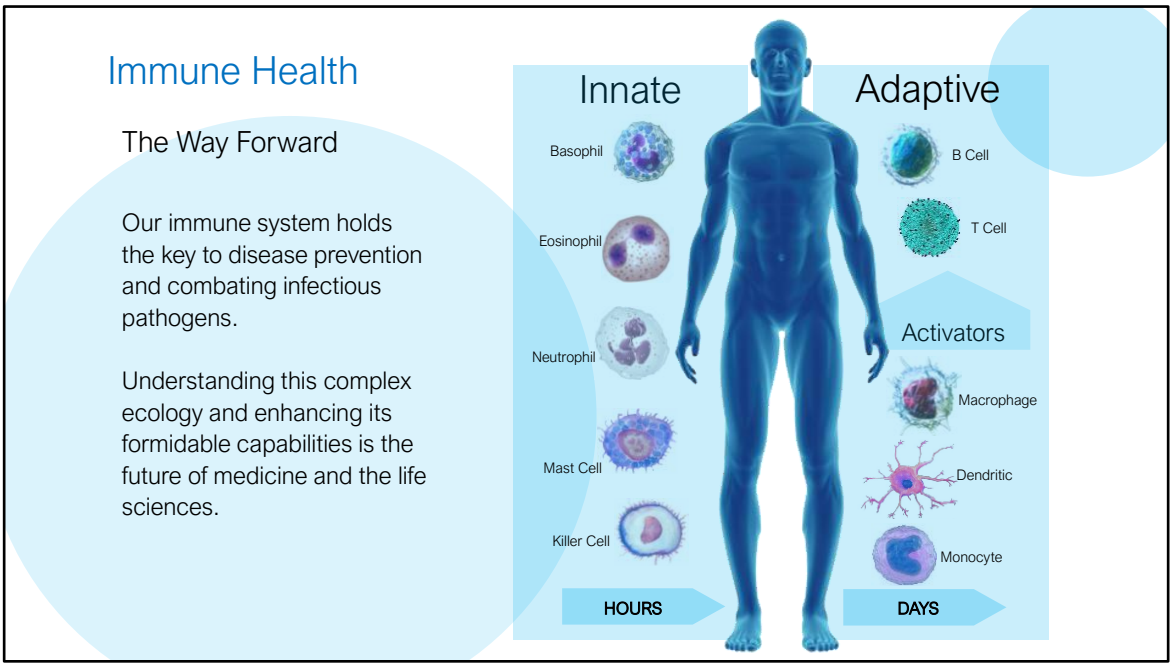


Every day we're exposed to pathogens of one form or another through contact, inhalation and ingestion. Nonetheless, we have a *remarkably* flexible immune system to protect us.



The built-in defense system we are born with is called innate immunity. This is our first line of defense against injury and invasion by pathogens.

- There are numerous types of innate immune cells with specialized functions, such as the ones pictured here.
- These cells broadly recognize pathogens, such as viruses and bacteria, as well as non-infectious problems and they respond rapidly in a manner of hours.
- Some innate immune cells are important for activating our 2nd line of defense, known as adaptive immunity.
- When the innate immune system is unable to contain an infection, the cells of the adaptive immune system step in as a second line of defense.

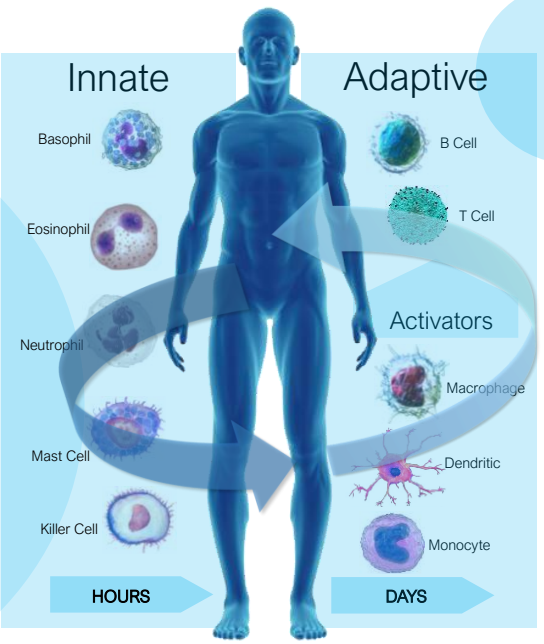


- Adaptive immunity develops and matures throughout our lives as we're exposed to pathogens, or, when we're immunized with vaccines.
    - Adaptive immune cells, such as B cells or T cells, are particularly specilazed to recognize specific pathogens.
    - This defense mechanism takes several days to develop but it provides long-lasting protection and quickly recognizes pathogens should they infect again.
- Vaccination, or immunization, is essentially a shortcut -- a way to train your immune system against a specific pathogen without actually becoming infected.

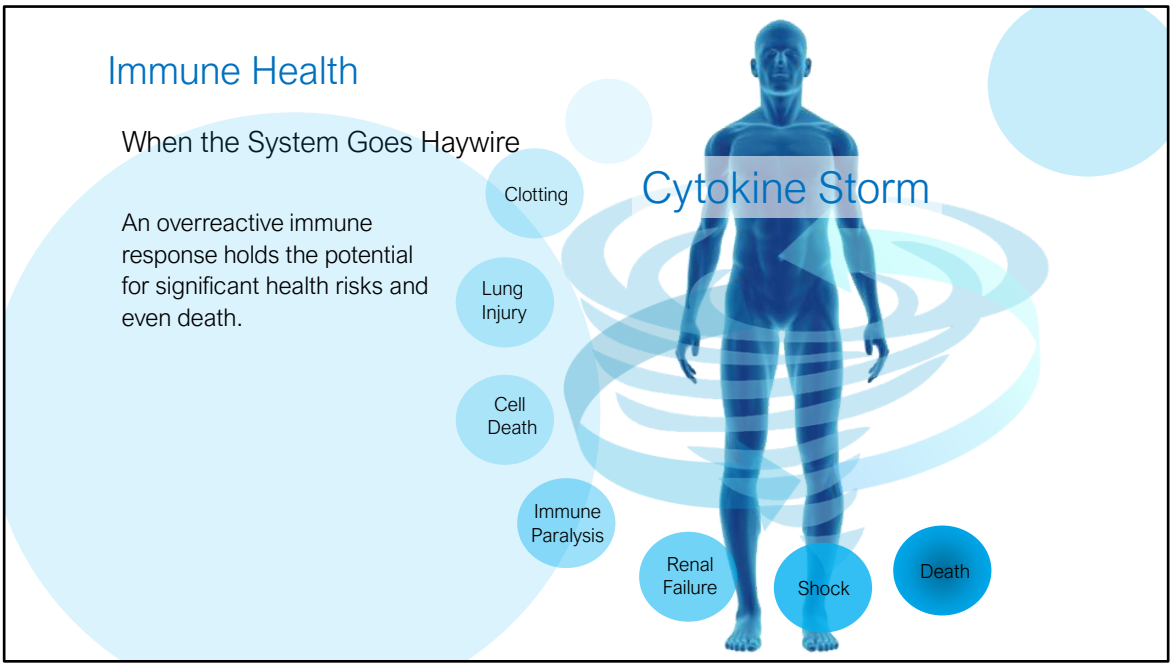
Immune Health

A Dynamic Balancing Act

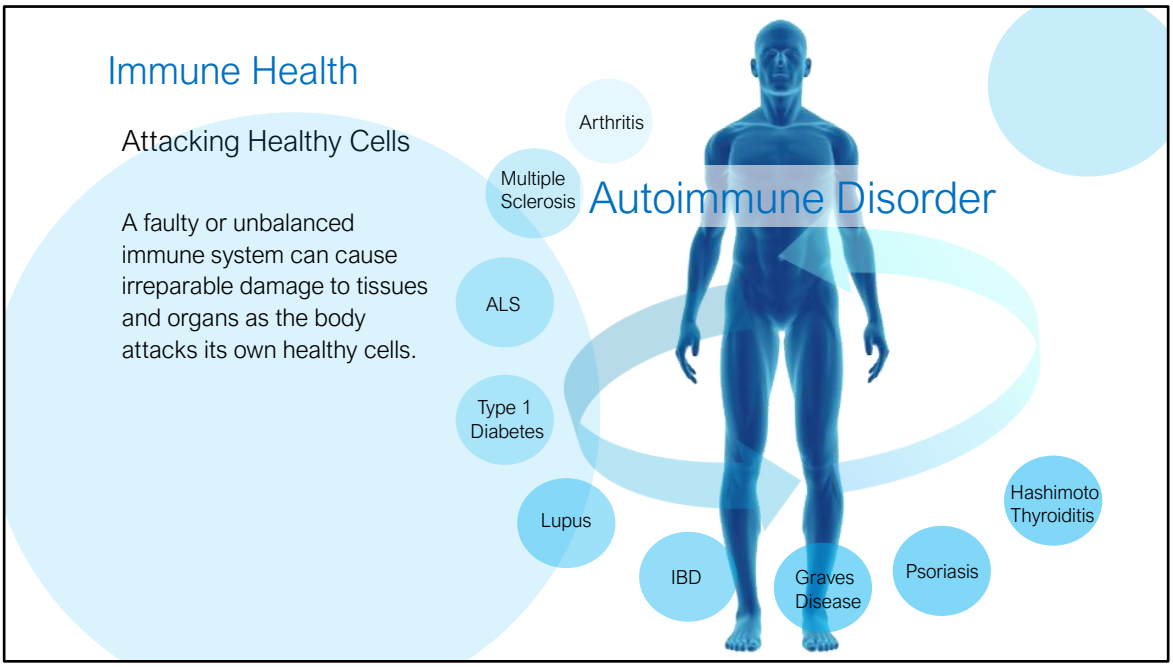
Innate and adaptive immunity work together to vanquish pathogens and provide healing relief to injured or infected areas.



- Optimal immunity is achieved only when the innate and adaptive systems work together to combat infection and minimize damage.
- Too much or too little of a response from either can be very harmful.



- Sometimes immune cells become hyper-reactive following an infection, causing an exaggerated systemic inflammatory response, or cytokine storm, which can result in serious complications and sometimes even death.
    - Examples of this include the acute lung injury caused by the influenza A virus or severe acute respiratory syndrome caused by the COVID-19 virus.
    - Sepsis is another life-threatening overresponse to infection. In fact, every year, more Americans die from sepsis than breast, colon, and lung cancer combined.



- Also, more than 80 types of autoimmune disorders result from an unbalanced immune system that attacks healthy tissue and organs, among them: multiple sclerosis, rheumatoid arthritis, lupus, Type 1 diabetes and inflammatory bowel disease.
- For those who suffer, the attacks can be unrelenting.

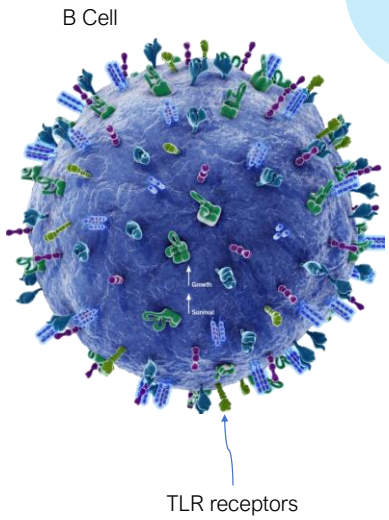
Immune Health

Toll-Like Receptors

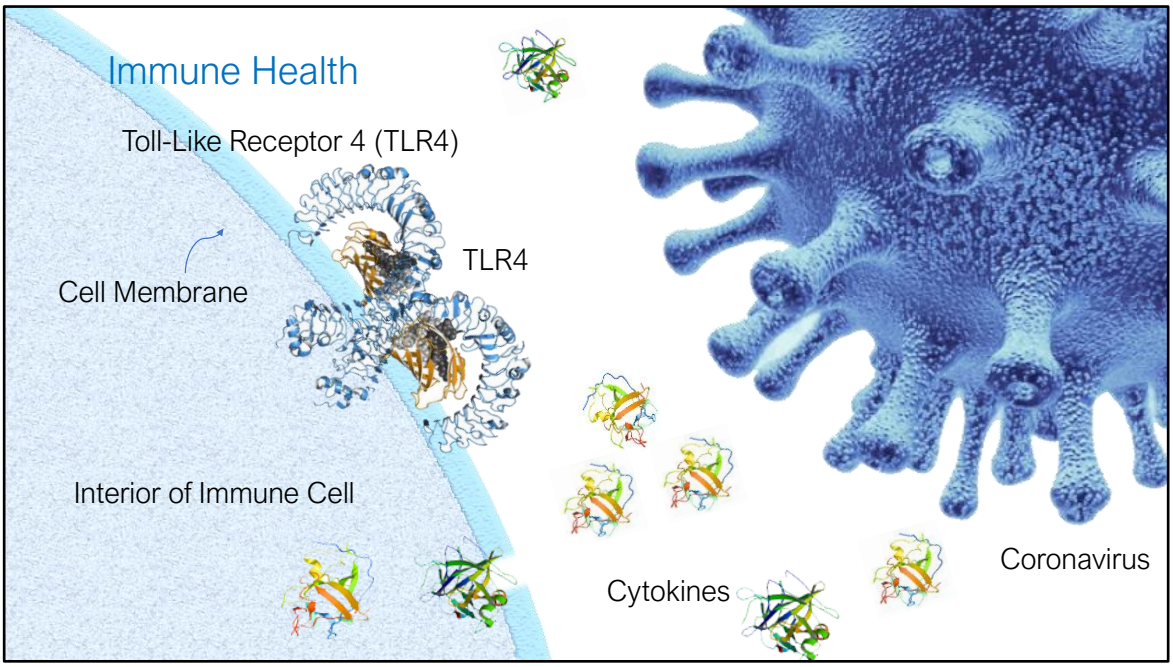
Detect bacteria, bacterial toxins, viruses, tissue fragments, necrosis

Activate release of cytokines and chemokines

Initiate Activator cells to trigger the adaptive immune system



- Years of research have uncovered the closely-linked complexity and layered defenses comprising our immune system.
- The most fundamental and well-studied components are the Toll-like receptors. These complex protein structures cover the surfaces of all immune cells, acting as sensors and messengers for both the innate and adaptive systems.
- Toll-like receptors detect a wide range of pathogens and injured tissues, sounding the alarm by releasing inflammatory cytokines – the chemical messages that regulate the immune response.
- They can also initiate activator cells to trigger the adaptive immune response and attack a targeted pathogen or to help mop up the site of an injury.



- Of the ten toll-like receptors present in the human immune system, Toll-like receptor 4, in particular, is involved in many acute and chronic diseases, including cytokine storms and autoimmune disorders.
- Its activation leads to inflammatory cytokine production, which in turn activates the entire innate immune response.
- The TLR4 receptor recognizes bacteria, viral proteins, polysaccharides, as well as proteins created by our own body, such as beta defensins and heat shock proteins.
- For this reason, TLR4 is an attractive target for non-antibiotic therapies to combat sepsis, asthma, allergies, chronic inflammation, viral infections and many autoimmune disorders.
- Although there's been some clinical research in this area, the landscape remains wide open for an effective therapy leveraging TLR4 and this is where ZIVO is primarily involved.
- Although ZIVO has focused its attention on animal health, the fact that we have conducted multiple successful clinical trials in animals, without observed side effects, bodes well for a potential human application.

Market Intelligence

Harnessing The Immune Response

Infectious Disease

Existing Products &
New Research

Vaccine Adjuvants

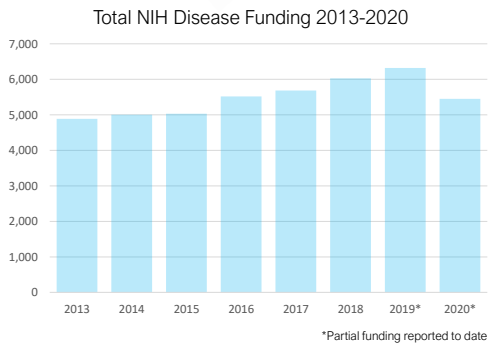
NOD-like receptor agonists

Immune Modulators

Interferons

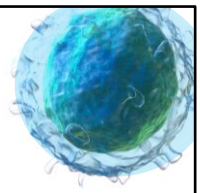
Innate Defense Regulator (IDR) Peptides

Microbiome Therapeutics



- Research scientists recognize the power of our immune system and look to harness it to treat or prevent disease while avoiding collateral damage or adding to the growing number of drug resistant pathogens.
- As we indicated earlier, vaccines have been in use for a century or more, but other immune therapies are available or actively being researched, such as vaccine adjuvants, immune modulators and microbiome therapeutics.
- Much of the public research funding for infectious disease, expected to reach $7 billion this year for the US alone, is focused on leveraging our own immune system.
- Private pharmaceutical industry investment is above and beyond this number.

Market Intelligence



Harnessing The Immune Response

Autoimmune Disorders & Disease

Existing Products & New Research

Steroids

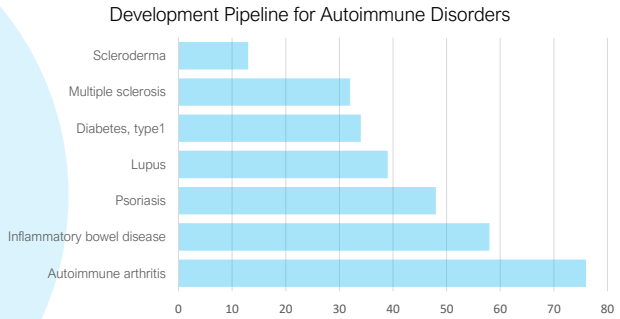
Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)

Interferons

Immunosuppressants

Monoclonal Antibodies

TLR Antagonists



- In terms of autoimmune disorders, doctors have relied on steroids, interferons, non-steroidal anti-inflammatory drugs or NSAIDs, and other drugs to attenuate the immune response, but research continues
- The development pipeline for autoimmune arthritis alone contains nearly 80 new drug candidates in various stage of development
- It's an extraordinarily large market with many opportunities for ZIVO

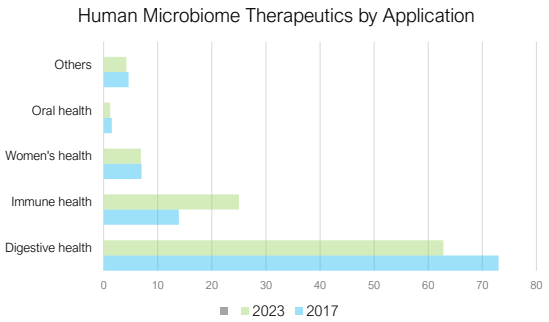
Market Intelligence

Global Market Trends

Market Size by Therapeutic in USD

Vaccines	$ 59.0B
Immunomodulators	$160.0B
Microbiome Therapeutic	$ 10.0M → $897.0M*
Autoimmune Therapy	$110.0B
Rheumatoid Arthritis	$ 22.0B

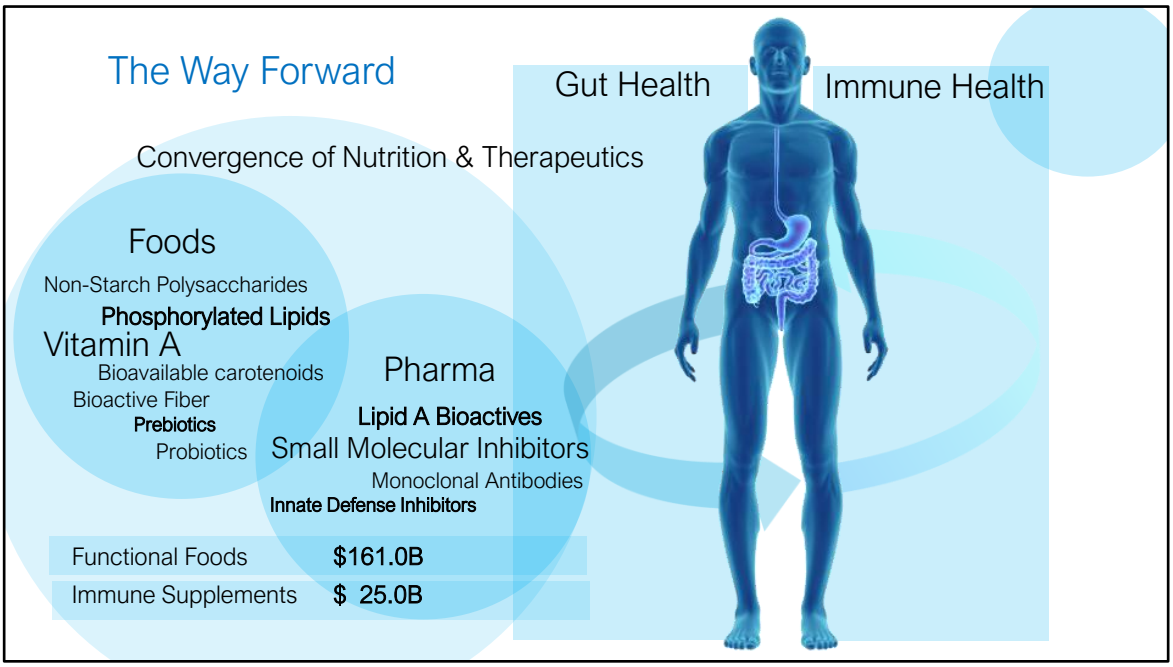
*Expected growth 2018 to 2025



The science and the direction of research, as discussed herein provides the trend and market opportunities. It's also important to provide context in terms of market size and adoption rates

- The **global vaccine market** is expected to reach total revenues of $59 billion by the end of 2020, nearly double that of 2014
- The **Immunomodulators market** was valued at roughly $160 billion in 2018 and expects to surpass $239 billion by 2026
- The **microbiome therapeutics market** is was valued at just US$ 10.1 Mn in 2018 and is expected to reach US$ 897.3 Mn by 2025. This is a vertical with intense activity with many candidates in different stages of development. ZIVO Bioscience is deeply engaged here as well, initially as it relates to poultry, to be followed by human research
- The **Autoimmune Market** accounted for $110 billion in 2017 and is estimated to reach $153 billion by 2025
- **And finally, the rheumatoid arthritis market** was valued at approximately USD 22.6 billion in 2018 and is expected to generate around USD 30.7 billion by 2025

These are substantial global markets where demand will only climb.



Going forward, what are the biggest, most far-reaching developments from our perspective?

Most importantly is the realization that much of our immune response is deeply integrated with gut health, which in turn is supported by a healthy microbiome

Immune modulation is an area of intense interest. It can be addressed both nutritionally and therapeutically. This area of convergence is where ZIVO may have the greatest impact and number of potential applications

From a market perspective, the biggest-selling drugs target immune disorders, immune stimulation or inhibition and other interaction with the immune system
The new drug development pipeline for immune products is active, but there haven't been any standouts relative to TLR modulation, which represents a singular opportunity for ZIVO

And, although we've focused on therapeutics in this presentation, this in no way minimizes the health benefits of nutritional products aimed at improving gut health and consequently, immune health, or market impact of such products:

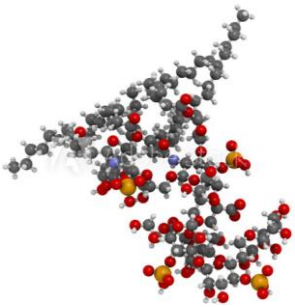
- The global functional foods market size was estimated at $161.49 billion in 2018 and is projected to reach USD 275.77 billion by 2025
- Likewise, the global Immune Health Supplements Market is expected to reach $25 Billion by 2025

We expect to be at the forefront of this convergence.

The Presenting Company

About ZIVO Bioscience, Inc.

- US-based biotech company creating breakthroughs to fight disease and infection
- Working to displace antibiotics and ionophores in the global food supply
- Developing a new approach to rheumatoid arthritis, sepsis, lupus, ALS and other immune disorders
- Accelerating development of a robust immune system in young animals, possibly young humans



ZIVO Bioscience is a US-based biotech engaged in the investigation of biologically derived and optimized candidates for medicinal and pharmaceutical applications in both humans and animals. ZIVO research and product development is focused on the general benefits of autoimmune and inflammatory response modulation. The Company has also developed nutritional products derived from its proprietary algal cultures for use as dietary supplements and functional food ingredients.

ZIVO Bioscience is actively working on approaches to displace or minimize antibiotics in the global food supply, accelerate development of a robust immune system in humans and animals, and develop new approaches to autoimmune disorders.

ZIVO is represented by IANUA Advisors, based in London.

Thank You

www.zivobioscience.com