***Program:*** Industrial Agriculture: Global Threat of Antimicrobial Resistance – Update 2020 (via Zoom)
***Speaker:*** Stephen J. Jay, MD, Professor Emeritus, Medicine and Public Health, IUSM
***Introduced by:*** Jeff Rasley
***Attendance:*** 88 (logged-in devices, sometimes more than one viewer per device)
***Scribe:*** Donald Mink
***Editor:*** Carl Warner

The Zoom copy of today's presentation lives on the Scientech Club website and can be accessed by clicking on: http://www.scientechclub.org/zoom/475.mp4

Dr. Stephen J. Jay's presentation is a follow up to a presentation to Scientech in 2011. His aims are to provide some history of how we got here, an update of the past decade and to reflect on our future threats and opportunities for creating a science-based paradigm shift to preserve lives, treasure and our humanity.

A short list of global health threats includes: pandemics, climate change, air pollution, loss of biodiversity with mass extinction and AMR (antimicrobial resistant) infections. There's commonality among these both in their origins and potential solutions. All are interrelated complex systems that require systems' thinking, planning and action. Underpinning these threats is our need for science-based policy to preserve our economy, security and public health. The National Academy of Sciences is concerned about America's eroding science education, leadership and investments, including the United States' decreasing global share of R&D. Ironically, a first ever Nobel Prize Summit to be held in April of this year to address our science shortcomings was postponed because of COVID-19. Scientists and public health experts agree that the intensity of COVID-19 in America is a result of the lack of science-based planning, leadership and action to contain the virus.

Today, there is a "perfect storm" from our "golden age of antibacterial (AB)" to a "post AB era" with marked increase in AMR and decrease in development of new AB classes. As we pressure 'bugs' with ABs, resistance increases. Yet new classes of antimicrobial agents and FDA approved ABs have plummeted. Legislation is critically needed to address this discovery void. Major drivers of AMR include increases in global meat consumption, population, income and urbanization. In 2019,

Princeton researchers found that increasing appetite for animal protein in low to middle income countries has tripled resistance in disease causing bacteria, (2000-2018) with "hot spots" in China, India, Brazil and Kenya. Livestock receive a smorgasbord of ABs. Like COVID-19 that respects no borders or political party, resistant organisms originating in Kenya or China WILL come to America with major implications for how we manage international relationships. Countries are part of a global tapestry, where a lethal virus or AMR bacterium in one country may reach all 195 countries in the world within days or weeks as has COVID-19. Our "perfect storm" has consequences: More than 60% of infectious disease doctors have treated patients with infections that didn't respond to any AB. We live in an era of "superbugs".

It's been known since the 1940s that resistant bacteria are produced by horizontal gene transfer where previously sensitive bacteria develop resistance, multiply and dominate. Today, the misuse of ABs creates AMR in humans, animals, and plants. For example, antimicrobials given to food animals quickly cause AMR that passes to the environment, to food, to humans who eat the food, causing often severe multi-drug resistant disease. Global spread of these organisms is ensured by international travel. Drug resistant microbes are widely dispersed in the complex web of societies: in humans, animals, health institutions, food, water, soil and manure. There are few places, if any, on earth where AMR organisms may not be found. The cost of AMR to global health and wealth is enormous. Renowned economist, Lord O'Neill, led a major study of the issue and estimated that, if

we don't act to stem the tide of drug resistance, there could be 10 million lives lost per year by 2050 (more than from Cancer) at a cost of $100 trillion of economic output. The 2019 CDC Report on AMR notes 2.8 million cases and 35 thousand deaths per year with annual costs of $55 billion. An AMR death occurs about every 15 min (For COVID-19, it's about 1 death per minute). You can see why hospitals are stressed.

Recent CDC guided infection control programs in hospitals have decreased AMR by 30%. The CDC advises us to: wash hands, improve AB stewardship, and expand tests and surveillance. Priorities include: eliminating ABs for growth promotion in food animals, creating infrastructure for tracking and monitoring AMR, speeding R&D for new agents and vaccines and importantly, improving international collaboration in monitoring and managing AMR. The reliance on classic ABs is giving way to the search for other molecular strategies to treat AMR infections. The stakes are high; we need new arrows in our clinical quivers. AMR threatens modern medicine putting millions at increased risk: those with chronic diseases, sepsis, surgery, cancer, dialysis, organ transplant. And COVID-19 is adding more than 40,000 new cases daily in America. Hospitalized COVID-19 patients often have viral pneumonia but are also at risk for bacterial pneumonia. We've known for years that viral infections such as (H1N1) increase this risk. Preliminary research shows that about 8% of hospitalized COVID-19 patients have bacterial pneumonia. But 30% of ICU patients have it; multi drug resistance (MDR) fatal outcomes are not infrequent. Despite the 8% rate of bacterial pneumonia, 70% of all hospitalized COVID-19 patients receive ABs which are in short supply in many hospitals. Research is critically needed to clarify optimum use of ABs in these patients. Both underuse and overuse of AB cost patient lives.

The dramatic shift in agriculture practices from pasture grazing in the 1940s to concentrated industrial animal feeding in recent decades has caused increased rates of disease in animals and humans. Discovery of new AM agents experienced a boom in early 1900s but has been followed by a bust. Nobel Prize winners Ehrilich, Domagk and Fleming gave us the arsenical drug Salvarsan, the sulfa drug Prontosil, and Penicillin. In the 1940s-50s, Penicillin was used to treat animal infections including cow mastitis. In his Nobel Lecture 1945, Fleming warned clinicians: "If you use Penicillin, use enough"; if you don't, you create drug resistant microbes. By the 1940s-60s, ABs were being used widely in animal agronomics. Farmers wanted to use low-dose AB in feed and water to enhance growth of animals and prevent infections. The major "con" was adverse health impacts—drug

resistance in humans. Farming practices began to collide with science 70 years ago and continues today.

There was no debate about using ABs prescribed by vets to treat specific infections. The conflict was: therapeutic vs non-therapeutic use of low-dose ABs: after surgery, for dry cow therapy, for stress of high-density confinement before transportation. In Europe, results in the '50s led to warnings and proposed regulations of farming practices. In major scientific reports in U.K., the so-called "corporatist" elites attacked the science and demanded "absolute proof" of causality (obviously impossible). They honed their denial strategies to "kick the can down the road" and stifle science-based regulations, a practice that continues today with parallels in how the U.S. has addressed other major public health threats: smoking tobacco, fossil fuels and air pollution, climate change and species extinctions. In 1961, Dr. Jevons, in London, discovered Methicillin Resistant Staphylococcus (MRSA) in a human skin infection and proposed likely point to point transfer. By mid 1960s, MRSA was endemic in U.S. hospitals and on farms. In 1972, Jevons work was confirmed: MRSA was indeed transmitted from farm animals to humans. In 1976, Dr. Levy's research echoed earlier evidence that AMR transmission may occur in humans exposed to food animals. Tetracycline in feed caused AMR that was transmitted from chicks to farmers.

Jay Sanford, a colleague of Dr. Jay, warned of MDR bacterial infections and established an AB stewardship program at Parkland Hospital (Dallas, Texas) in the '60s to improve AB use. It was 2014, when President Obama issued an executive order for an AB stewardship program that's used in most hospitals. From 1972-1977, the FDA recommended that sub-Rx ABs in food animals be documented. Their recommendations were not implemented, and since 1977 science- based action to improve health safety have been stymied at the FDA and in Congress. A false dichotomy, "public health vs wealth" has been a common theme in Congressional debates, similar to what we hear today about COVID-19 and climate change. The good news is the FDA, CDC, USDA and other health- related fed agencies all agree with decades of science regarding human harm of sub- Rx AB in food animals. In 2006, Robert Martin at PEW Charitable Trusts received a Bloomberg School of Public Health grant to study AB use in industrial farm animal production. In 2008 testimony to Congress, he showed the wealth of evidence supporting the phasing out of non-Rx use of AB in food animals, closing loopholes in regulations, improving monitoring and reporting of AB use and improving monitoring rates of resistance in food, food animals, the environment and humans, and providing oversight of AM use. Based on these recommendations, the *Preservation of Antibiotics for Medical Treatment Act* was introduced in 2007; it's been re-introduced in every Congressional session since then. There have been many co-sponsors of this science-based bill but no action.

PEW Charitable Trusts leadership in science- based advocacy has increased. In 2010, Dr. Jay participated in a Capitol Hill briefing: "Alternative to AB use in Farm Animals" and also submitted testimony for Congressional hearings from April-July 2010. At the time of these hearings, there was major science, public health and public support for addressing AMR. The FDA issued Guidance #209 that confirmed their agreement with the science of AMR. Unfortunately, they offered no urgency in meeting science standards. The Guide was voluntary and used ambiguous (loophole- filled) language, e.g., "Judicious use of AB's." The good news was FDA had outlined the strong basis for regulations and many in farming industries supported these conclusions and recommendations for action and change. Since 2010, there's been slow progress but reason for optimism that the U.S. and global community will create evidence-based public policy on this issue soon. The FDA's 5 year plan (2018-2023) outlines evidence-based strategies adopted about twenty years ago in Denmark and U.K. Complex systems' problems, such as AMR in food animals, require systems'-thinking and system based solutions. In the U.S. this includes strengthening AB stewardship, veterinary oversight of drug use, updating "medically important" ABs and AB labels with clear definitions and duration of use of the AB. Also critical, the creation and reporting of the animal biomass method and new

investments in R&D for alternatives to ABs. It's unknown how the COVID-19 pandemic economic downturn and national angst will impact progress on the FDA 5 year plan.

Veterinary oversight of AM use in Denmark has shown that AB use can be decreased significantly while increasing production of food animals. Antimicrobial growth promoters and veterinary prescribed AMs decrease, while pig production and exports increase. PEW Trusts offers five priorities for combating ABR. First, reduce AB use in human medicine; physicians are making progress although about 30% to 50% of outpatient AB prescriptions are unnecessary or inappropriate. There are marked unexplained regional differences in prescribing. For example, Indiana rates are much higher than California, and rates in the South are significantly higher than the rest of the U.S. PEW's second priority is to improve AB use in animals. Third, fix the broken AB market with legislation to spur development of new AB. Fourth, improve stewardship and innovation. And fifth, expand international collaboration to control global spread of AMR organisms.

A major impediment to progress is the long-standing FDA policy of voluntary guidelines. We're witnessing a public health failure with COVID-19, in part, because of failure to create a national plan with specific guidelines for interventions and requiring adherence to them with incentives and penalties for non-compliance. Fuzzy language and definitions in FDA Guides have provided

loopholes that are used to avoid change. The CDC in 2019 outlined steps needed to prevent and slow spread of infections: vaccination, hand and respiratory hygiene, cleaning and disinfection; biosecurity measures on farms and quick response to unusual genes and germs. The CDC AMR Lab Net has been established and provides comprehensive DNA sequencing and data for response and prevention, a strategy to move current science into the field, hospitals, clinics, and health departments. Artificial Intelligence is creating new ABs, and, MIT has used machine-learning to create Halicin.

In conclusion, Dr. Jay noted that there's similarity with AMR and our other global health threats, including COVID-19. There's commonality in their origins, exponential trends and potential solutions. Bringing science, law, and wisdom to bear will not be easy. We need systems-thinking and action. These are cautionary tales of how disease, suffering and costs are experienced when investments in science and public health are neglected. As a physician, Dr. Jay favors a science-based solution. The math of exponential growth is the headwind that may limit our success: Finite resources but logarithmic population growth. In a famous 1969 lecture Albert Bartlett said: "The greatest shortcoming of the human race is our inability to understand the exponential function." This shortcoming has been on vivid display in society's response to the above crises. How will humanity manage our great dilemma of finite resources in the face of exponential population growth? Finally, the question is "Does America have the political will to lead the global response to our existential threats?"

**Stephen J. Jay, MD**
(Photo courtesy of Fairbanks School of Public Health)