Article: "Ribosome-targeting antibiotics and mechanisms of bacterial resistance."
Wilson, Daniel. Nature Reviews Microbiology volume 12, pages 35–48(2014).

What are some other approaches for selectively killing pathogenic microbes in a human host, besides antibiotics?

With the devastating COVID-19 pandemic and other recent infectious pathogens or viral diseases (Ebola, Zika, etc.) combined with an increasing rate of resistance to conventional antibiotics, several antibacterial and antiviruses strategies have been developed.

Regarding bacterial therapeutics, treatment strategies include:

Targeting toxins and secretion systems: Secretion systems transport toxins produced in the bacterial cytosol bacteria across the bacterial cell membrane to human cells. Two types of agents exist: chemical inhibitors and antibodies which block host cell receptor or disrupt the pore formation which allows the toxin to penetrate the infected cell. Inhibitor drugs target type 3 secretion (T3S) systems used by many gram-negative bacteria to inject these toxins directly into human cells. More specifically, a number of agents are studied in clinical trials to target either proteins *PscF* which form the T3S needle complex, or *PcrV*, a protein part of T3S apparatus critical for insertion of a translocation pore into the host plasma membrane or even the host infected cells directly. However, bacteria often use multiple and redundant pathogenic pathways and, in combination of conventional antibiotics, combining multiple compounds directed to several bacterial targets may be necessary for greater efficacity.

Targeting biofilms: new methods are being investigated to prevent or disaggregate biofilms which are major sources of infection. Small molecules or compounds have been developed to interfere with molecules which regulates bacteria to form biofilms (for example c-di-GMP, a signaling molecule or adhesins).

Targeting signaling: quorum sensing (QS) plays a major role in biofilm formation and regulate the virulence of the bacterial infection. The existing drug strategies aim at inhibiting directly the synthesis of QS molecules or prevent their binding to their receptors. Other inhibitors block the upstream regulatory system necessary for the transcription of virulence factors.

Bacteriophage therapy: bacteriophages are attractive therapies as they have no effect of human cells, or microbiome and are very specific to a strain but they also can develop bacterial resistance, are difficult to produce and deliver to the human host, and usually needs to be bundled with others due to their specificities.

Microbiome therapy: fecal microbiota transplant (FMT) or the use of probiotics have shown to cure many patients; they are too novel and raise many questions.

There are two types of antiviral therapeutics: directly targeting the virus (antibodies, receptor decoys, polymerase inhibitors, viral protease inhibitors, nucleoside analogs, viral translation inhibitors, fusion inhibitors) or the host cells (antibodies, endocytosis inhibitors, interferons,

kinase inhibitor, lipidomic drugs). With progress in sequencing technologies, many viral genome sequences have been identified providing a vast range of various strains for drug and vaccine. Using reverse genetic, synthetic biology has generated reporter viruses used to identify strains capable of replicating in human cells. RNA-based therapeutics are promising for preventing and treating viral diseases. They are simple to design, could be reconverted quickly in response to new viral sequences, deactivate either viral or host replication factors, interfere with regulation or restriction factors. RNA-based therapeutics include: antisense oligonucleotides (ASOs), anti-micro RNAs (anti-miRs), RNA aptamers, miRNAs/siRNAS, small acting RNAs (saRNAs), mRNAS and CRISPR RNAs.