Malaria and trypanosome eukaryotic protozoan pathogens are complex and encode ~5,300 and ~10,000 genes, respectively. They develop in and transit through their mosquito and tsetse fly insect vectors which transmit these parasites to humans. Both parasites evolved metabolic and developmental adaptations that enable their survival in the environments that differ between the insect vector and the human host. These adaptations are controlled by the pathogens’ cellular regulatory processes. Both parasites evade the host immune system via surface antigenic variation, which has similar features in both parasites. Malaria resides intracellularly in the human host, which aids immune evasion, but the (African) trypanosome is exclusively extracellular. Although drugs have been developed, more are needed for both diseases. Developing a vaccine for trypanosomes appears unlikely but developing vaccines for malaria looks promising, albeit complex.