Strategic Areas

Addressing global health challenges

We need to stop thinking about diseases as silos and start thinking more transversally. If we start to look transversally at the problems we’ve got and the solutions that may exist outside our field, then we can begin to address big healthcare issues.

David Reddy
CEO, Medicines for Malaria Venture

2018 highlights

• Committed to invest USD 100 million over the next five years to advance R&D of new antimalarials
• Delivered nearly 900 million treatment courses of Coartem, including 370 million courses of the pediatric formulation, without profit
• Continued providing multidrug therapy for leprosy, free of charge, reaching a total of 7.2 million patients since 1999
• Collaborated with Microsoft and the Oswaldo Cruz Foundation, using AI in the early detection of leprosy
• Initiated collaboration with health authorities and local partners in Ghana to launch our commitment to sickle cell disease in Africa
• Launched a new partnership with the World Heart Foundation to develop a roadmap to address Chagas disease in Africa

Key challenges

• Challenges in maximizing the potential success of our R&D portfolio for antibiotics resulted in an out-licensing and equity agreement
• The global response to malaria elimination seems to have stalled, while the threat of parasite resistance to existing therapies remains strong
• There is reduced awareness in political and health communities about the need to continue efforts toward full leprosy elimination
• Extremely limited newborn screening services for sickle cell disease mean diagnosis often happens too late, resulting in high mortality for children under 5 years old
**Our approach**

Novartis has a long heritage in tackling neglected tropical diseases, with two flagship programs targeting malaria and leprosy. To date, nearly 900 million treatment courses of our antimalarial, Coartem, including 370 million courses of a unique child-friendly formulation, have been delivered without profit, and approximately 60 million multidrug therapies for leprosy have been donated through the World Health Organization (WHO).

We also have a longstanding investment in research for various infectious and neglected diseases through the Novartis Institute for Tropical Diseases (NITD), which was founded in 2001 and is dedicated to finding new medicines for these diseases. In 2018 Novartis investment, including NITD, was more than USD 24 million, up very slightly on 2017. We continue to make strides against various infections, including malaria, African sleeping sickness, leishmaniasis, Chagas disease and cryptosporidiosis (diarrheal disease).

Drug discovery efforts at NITD have delivered an industry-leading pipeline of drug candidates to anticipate the emerging threat of artemisinin resistance and to support the malaria elimination agenda. Two drug candidates, KAE609 and KAF156, as well as an innovative formulation of lumefantrine are currently being evaluated in Phase II studies. These programs are conducted in partnership with the Medicines for Malaria Venture. In parallel, we are feeding the pipeline with new candidates that have a fast-acting blood-stage antimalarial profile. The current frontrunner compound and other related analogues are being investigated.

In April, we communicated our intention to invest more than USD 100 million over the next five years to advance research and development of new antimalarials, expand access to pediatric antimalarials, and invest in health infrastructure in Africa. This investment is meant to advance the Novartis malaria pipeline through 2023 and to complete comprehensive global clinical trial programs for KAF156 and KAE609. The investment also includes new uses of technology to identify areas where the malaria burden is greatest. This information could be used to support capability and capacity building to establish future clinical trial sites where medicines could be evaluated in the populations where they are most needed.

Novartis is a signatory to the London Declaration on Neglected Tropical Diseases, which aims to control, eliminate or eradicate 10 diseases by 2020. In line with our reaffirmed commitment, NITD and the Genomics Institute of the Novartis Research Foundation (GNF) have developed, in partnership with the Wellcome Trust, a promising portfolio of novel drug candidates for the treatment of three kinetoplastid diseases: human African trypanosomiasis (sleeping sickness), leishmaniasis and Chagas disease. GNF recently advanced LX408 as a promising drug candidate for the treatment of visceral leishmaniasis, and Novartis is in advanced discussions with the Drugs for Neglected Diseases initiative to partner on the clinical development of this compound. NITD will also explore opportunities to collaborate with other relevant research groups within Novartis to target the host response in chronic stages of Chagas and leishmaniasis. Together with our leprosy elimination effort, this strategic focus on kinetoplastid parasitic diseases would address four out of 10 diseases in scope of the London Declaration.

**Why is it important?** While the relative burden of noncommunicable diseases in developing countries is increasing significantly, there remains an unfinished agenda to control and eliminate tropical infectious and other neglected diseases. Neglected tropical diseases still affect over 1 billion people, and the recent World Malaria Report points to evidence that the global response to the fight against malaria has stalled.
Diarrheal diseases are increasingly recognized as a leading cause of mortality, and cryptosporidium infection is a major pathogen responsible for diarrhea-associated death in young children in developing countries. Through an exploratory effort leveraging the results of our malaria research program, we recently identified the apicomplexan PI4K inhibitor KDU731 as a potential drug candidate for the treatment of cryptosporidiosis. The Bill & Melinda Gates Foundation supported the preclinical development of KDU731. Based on our learnings in the course of research and early development efforts in cryptosporidiosis, we may consider infectious diarrheal diseases more broadly in the mid to long term as part of our work to tackle global health issues.

In 2016, the WHO updated its guidelines for multidrug-resistant tuberculosis to include our medicine clofazimine as a recommended drug of choice. Further, in 2018, the WHO issued a rapid communication with revised guidance on tuberculosis, specifically on the longer regimen to treat multidrug- and rifampicin-resistant tuberculosis, prioritizing oral agents over injectables. Clofazimine is recommended as part of this revised regimen.

Accordingly, Novartis has been working to expand the clofazimine label to include this indication; clofazimine is currently only approved in combination with rifampicin and dapsone as a treatment for leprosy. The goal is to provide an affordable treatment in countries where tuberculosis remains prevalent. We recently upgraded our manufacturing capabilities in China to support this effort.

Novartis is continuing its partnership with the WHO to provide clofazimine, as part of a multidrug therapy, free of charge for leprosy patients in various lower-income countries. In addition, in 2017, Novartis began supplying clofazimine to partners (including the Bill & Melinda Gates Foundation, the Liverpool School of Tropical Medicine, and the Wellcome Trust) to investigate its use to treat cryptosporidiosis in people with HIV/AIDS in Malawi. This work continued throughout 2018.

Novartis is a co-founder and a member of the Swiss Alliance against Neglected Tropical Diseases (SANTD), a consortium of 12 Swiss nongovernmental organizations, educational institutes and pharmaceutical companies that have joined forces to combat neglected tropical diseases.

Helping address the needs of children
Children are not small adults when it comes to clinical pharmacology; they require treatments that are adapted in terms of regimen, dose and formulation. In recent years, progress has been made in the development of pediatric formulations, and advances have enabled greater dose flexibility, easier administration, and better tolerance by children. However, new pediatric formulations only address a small part of all therapeutic needs in children. Further, despite a reduction in child mortality by more than half since 1990, infectious diseases – including serious bacterial infections such as pneumonia and sepsis – continue to take a significant toll on children.

Responding to the call from UNICEF to combat childhood pneumonia, Sandoz developed pediatric amoxicillin, today recommended by the WHO as first-line treatment for childhood pneumonia. Over the last three years, Novartis Social Business has supplied more than 3 million pediatric amoxicillin treatment courses to UNICEF and Médecins Sans Frontières. Novartis is now also active in the fight against childhood pneumonia through the Every Breath Counts Coalition, a global network established in 2018. Coalition partners, representing more than 30 organizations, are working to help target and increase investments for pneumonia prevention, diagnosis and treatment to help end preventable child pneumonia deaths by 2030. Expanding pneumococcal vaccine coverage will be a top priority, along with increasing access to better diagnosis and treatment tools, including pulse oximetry, child-friendly amoxicillin and oxygen.

In September, we announced a partnership with the Global Antibiotic Research & Development Partnership to accelerate the development and availability of generic antibiotics to help reduce child
deaths from drug-resistant infections. We are aiming to improve and adapt existing generic antibiotic formulations and dosing regimens for newborns and children. In particular, development will target heat-stable pediatric formulations against bacterial infections – a leading cause of death in children under age 5 in low- and middle-income countries.

**Tackling leprosy elimination**
Taking another step in our fight to eliminate leprosy, the Novartis Foundation was a founding member of the new Global Partnership for Zero Leprosy. It aims to accelerate progress toward a world without leprosy by coordinating research activities, strengthening existing national leprosy programs, and increasing advocacy and fundraising.

Since the introduction of multidrug therapy in 1981, the global burden of leprosy has been reduced by 99%. Novartis has donated multidrug therapy through the WHO since 1999, reaching more than 7 million patients worldwide. However, to finally eliminate leprosy, innovative solutions are required. The Novartis Foundation and Microsoft are partnering to develop a proof-of-concept digital health tool, enabled by artificial intelligence, and a Leprosy Intelligent Image Atlas – in collaboration with local investigators from the Oswaldo Cruz Foundation (Fiocruz) in Brazil – to aid in the early detection of leprosy. The launch of the first public version of the atlas is planned for 2019. The foundation has also been working with research partners to develop a leprosy diagnostic test. The hope is that, once this test is developed, leprosy will be diagnosed before significant nerve damage has occurred and the disease is transmitted to others.

**Partnering on Chagas and sickle cell disease**

In Latin America, we kicked off a new partnership with the World Heart Federation to develop a roadmap for addressing Chagas disease, the second most common cause of chronic heart failure in Latin America, affecting 8 million people in 21 countries. We also convened a two-day workshop at NITD in June that was attended by 15 expert parasitologists and physicians from around the world to discuss future drug discovery strategies for Chagas disease and leishmaniasis. Learnings from this event will help inform our R&D activities.

In Africa, we kicked off an effort to establish and strengthen partnerships around sickle cell disease (SCD), with the aim of understanding and helping address unmet needs. SCD is recognized by the World Health Assembly as a public health priority and is a neglected health problem in sub-Saharan Africa. Approximately 80% of individuals with SCD globally live in sub-Saharan Africa, and more than half of affected individuals die before age 5 due to preventable complications. The goal is to apply our learnings and expertise to create a holistic approach to help local partners tackle the disease over the next few years.

We took several steps in 2018 to facilitate this learning. A cross-functional team from Novartis visited Ghana for a week in April, meeting with multiple academic groups, the Ministry of Health, and representatives from hospitals, clinics and newborn screening sites, among others. In May, in parallel with the World Health Assembly, we convened a roundtable event in Geneva, Switzerland, that was attended by SCD stakeholders from six African countries. Additionally, in late October, Novartis Social Business hosted a workshop in Ghana to discuss opportunities to introduce hydroxyurea, a generic medicine that is used to treat SCD.

In 2019, we aim to launch our commitment to SCD in Africa, starting in Ghana, where we are already working with health authorities and local partners to develop a comprehensive and replicable model for improving access to medicines and care for patients with SCD. The collaboration is to include supporting the Ministry of Health and Ghana Health Service in establishing 10 SCD centers across Ghana, field-testing treatment guidelines and implementing a newborn screening program at the national level. At the same time, we submitted a registration dossier for hydroxyurea to treat SCD in Ghana and Kenya. In October, the Ghana Food and Drugs Authority approved hydroxyurea for the treatment of SCD. We anticipate the
medicine to be available there in 2019, marking the first time that hydroxyurea is provided to patients for this indication in Ghana.

**Addressing drug resistance**

Antibiotics are the cornerstone of modern medicine and have saved countless lives since their discovery. However, their effectiveness is being threatened by multidrug-resistant bacteria, and both their overuse and misuse contribute to the problem.

Antimicrobial resistance (AMR) is recognized by the WHO as one of the major threats to global public health. The Global Action Plan on AMR states that, without harmonized and immediate action on a global scale, the world is heading toward a post-antibiotic era in which common infections could once again become leading killers. It is estimated that AMR could lead to 10 million more deaths annually by 2050.

As a society, we must better safeguard the medicines we have today. We cannot just rely on new antibiotics coming to the rescue. A lot needs to be done, and we will undoubtedly achieve more working together than in isolation.

Sandoz, our generics division, is the world’s largest provider of high-quality, affordable antibiotics. Today, 90 million patients in 130 countries receive treatment with antibiotics provided by Sandoz for a wide range of infections. We therefore recognize the need to find the right balance between improving access to existing antibiotics and ensuring that they are used in a responsible and sustainable way. Sandoz is actively involved in global and local partnerships to help ensure the responsible and appropriate use of existing antibiotics in line with the WHO guidelines.

For example, in 2015, Sandoz in Latin America created Better Care More Health (or Mejor Cuidado, Más Salud), an ongoing multimedia educational campaign on responsible antibiotic use, targeting physicians and pharmacists in eight Latin American countries. Sandoz is currently partnering to create a website and mobile app focused on AMR, with the aim of addressing prescriber needs for continuous medical education, and providing simple and efficient access to prescribing guidelines. In addition, Sandoz regularly organizes events to share medical information about appropriate antibiotic use across different regions, such as Central and Eastern Europe, the Middle East and Africa, including remote locations. It uses multichannel platforms to reach healthcare professionals.

In July 2018, Novartis announced the decision to exit antibacterial and antiviral research. While the science for the impacted programs was compelling, the company decided to prioritize its resources in other areas where it believes it is better positioned to develop innovative medicines that could have a positive impact for patients. However, the need for antibacterial and antiviral medicines is clear and, to maximize the chances that these programs will one day help patients, Novartis is actively engaged in out-licensing with companies focused on developing medicines in these areas.

In October, we announced a licensing and equity agreement with Boston Pharmaceuticals for the development of three novel anti-infective drug candidates in the Novartis portfolio that have the potential to treat antibiotic-resistant infections.

- **LYS228** is a potential best-in-class monobactam that has entered clinical development and has demonstrated activity against carbapenem-resistant enterobacteriaceae (CRE) with resistance caused by serine beta-lactamases and/or metallo-beta-lactamases.
- **IID572** is a novel beta-lactamase inhibitor that may be used in combination with LYS228 or other beta-lactam antibiotics to expand their use against difficult-to-treat infections caused by a broader spectrum of CRE.
- **MAK181** is an oral, potentially first-in-class LpxC inhibitor for pseudomonas infections.

In December, as part of our strategy to partner and share data with external innovators committed to developing medicines that address global health challenges, we contributed data from...
our antibacterial research programs to the Pew Charitable Trusts’ Shared Platform for Antibiotic Research and Knowledge (SPARK). Specifically, we transferred data sets from our LpxA, LpxD and LpxK programs, which are focused on attacking Gram-negative bacteria – a class of pathogens with tough defense mechanisms that comprise some of the most dangerous superbugs. SPARK is a cloud-based platform that brings together chemical and biological data from published studies and previously unpublished work focused on addressing antibiotic resistance. It is open and accessible to researchers around the world.

Novartis remains committed to innovation, with its pledge in April to advance the Novartis malaria pipeline through 2023; malaria is identified by the WHO as an area at risk from AMR (see page 30 of this report). Sandoz is also intensifying its focus in the area of non-traditional R&D to explore innovative solutions that could prolong the life of existing antibiotics and improve patient adherence to therapy to safeguard future antibiotic effectiveness.

Photo  Dr. Yifter leads a weekly training session for medical students. As one of the few endocrinologists in Ethiopia, she knows it is imperative to train the next generation of doctors.