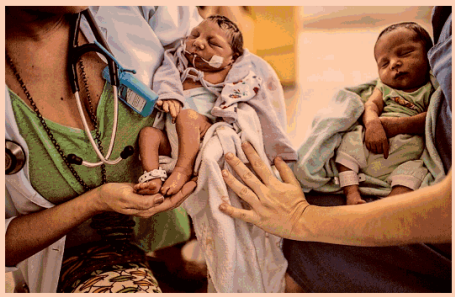
Mayana Zatz Her work on twins shows a genetic component to the birth defect, says *Andres Schipani*

Brazilian team finds clue to congenital Zika syndrome



Mystery: Mayana Zatz (bottom right) tested non-identical twins where only one of the pair had the Zika birth defect (above left, top) — Hilaea Media/Dado Galdieri for Financial Times

Soon after the Zika epidemic broke out in Brazil, Mayana Zatz — an acclaimed geneticist who, for the preceding four decades had been tracking rare genetic disorders that destroy muscles — received a surprise phone call from the scientific director of a research foundation in São Paulo.

Carlos de Brito Cruz told her Brazil was in a crisis and asked if she could contribute in any way.

It was 2015, and scientists were trying to establish a link between the Zika virus — usually a mild condition that can cause flu-like symptoms — and a horrifying birth defect called microcephaly in which babies are born with abnormally small heads. The affected children also face a lifetime of mental disabilities, seizures, as well as hearing and sight problems.

Prof Zatz's first thought was: "I am not an infectologist, I have nothing to do with this."

Over the years, she and her team at the Human Genome Research Centre had helped close to 30,000 patients, after identifying genes responsible for muscular dystrophies, mainly neuromuscular.

"But [after hearing more about the birth defects] this caught my eye right away because only a small percentage was suffering from it." She immediately began to wonder whether there was a genetic component to the condition, so she rounded up her team and started looking for twins in Brazil's worst-affected areas.

"What interests us very much is what protects some people from the effects of mutation," says Prof Zatz, a larger-than-life 70-year-old, who has won accolades for her work as a scientist (see box).

Despite her scientific achievements, this new assignment was very different to the work she had been doing before. "This was completely out of her scope of action, she has never worked specifically with virology, but her acumen on this was incredible," says Ernesto da Silveira, a biological engineer who is a member of her team in the Zika project.

The scientists identified Brazilian twins whose mother had been exposed to the Zika virus. Two pairs were identical and the rest were non-identical.

The identical twins all had microcephaly, but of the seven other pairs of non-identical twins, only one pair of twins was both affected.

The remaining six pairs were "discordant", with only one child presenting with microcephaly, even though they had shared the same uterine environment.

"She got that stuck into her head, called us and said: 'Let's design a project, I think there is something there'," Mr da Silveira says.

Prof Zatz and her team went to Recife and interviewed and examined the families and twins, with particular interest in the patients she called *discordantes* or anomalous — that had one twin affected while the other was not.

To identify any possible genetic component, her team compared all the gene sequences from eight pairs of twins and 10 other babies that developed the Zika syndrome.

They found that between 6 and 12 per cent of the babies born from mothers infected with the Zika virus had what Prof Zatz calls "congenital Zika syndrome".

"[Even] if the baby has these genetic susceptibility factors, we believe the baby will not have microcephaly unless the baby is infected by the Zika virus," Prof Zatz explains.

The results, published in Nature earlier this month, confirm the hypothesis of a genetic influence on susceptibility to the congenital Zika syndrome and microcephaly, she says.

More than that, it suggests that there could be a value in taking this line of research with other diseases.

"This [work] shows that genetics and infectious diseases can have an intersection," Prof Katz says.

"We could identify the people with the genetic alteration and prioritise them in a future vaccine strategy. Same with mothers who are pregnant and have exposure to Zika, if they don't have this gene, they do not have to worry," says Prof Zatz, who has two children and has two grandchildren.

Since the outbreak, Zika has receded as people build up resistance to infection and authorities have been fighting the Aedes aegypti mosquitoes that spread the virus.

Brazil declared an end to its Zika emergency in May last year after recording a 95 per cent fall in the number of cases in the first four months of 2017 compared to the previous year. However, the virus remains a health threat in the region and a return could affect future generations.

The World Health Organization announced last year that 31 countries had reported microcephaly cases, or central nervous system malformations, potentially linked to Zika.

CV Mayana Zatz

BORN
July 16, 1947, Tel Aviv, Israel. She moved with her family to Paris the following year and arrived in São Paulo in 1955.

EDUCATION
Bachelors in biology and PhD in human and medical genetics at University of São Paulo, post-doctoral research in medical genetics at UCLA.

TO STAY OR GO
She had several offers to stay on and work in the US, but decided to return to Brazil where she felt she could "make a difference".

She returned to São Paulo to focus on the diseases that cause muscular dystrophy: "Nobody worked on that here then," she says. She went on to pioneer the use of molecular biology in Brazil's fight against rare diseases.

CAREER HIGHLIGHTS
1982 — 1992
Assistant professor of human and medical genetics, University of São Paulo
1992 — present
Professor of human and medical genetics, University of São Paulo
2000 — present
Director of the Human Genome and Stem-Cell Research Centre (Hug-Cell), University of São Paulo
1996 — present
Member of the Brazilian Academy of Sciences
2005 — present
Member of The World Academy of Sciences (TWAS), a Trieste-based institution that fosters science in developing countries
1981 — 2015
Founder and president of the Brazilian Muscular Dystrophy Association (ABDIM)
2010 — 2012
Board of revisers (BORE) for Science, the scientific journal

INTERESTS
Her interests include jogging, travelling, watching films and going to the theatre.

Chinese rare disease patients 'waiting for death'

Costs

Recent moves by Beijing could open the door to wider coverage, say *Tom Hancock* and *Wang Xueqiao*

Li Wenyan was unable to afford medical bills for her seven-month-old daughter's rare disease, which could cause her heart to fail within months. So she turned to a new source of funding: asking strangers for money on the internet.

"I come from generations of peasants and my family has an annual income of Rmb30,000[$4,730]," Ms Li wrote in a post on a crowdfunding site. She added that treatment costs were Rmb120,000 a month and with "debts piled high I have no other option," alongside two emojis showing hands clasped in prayer.

The campaign attracted more than 1,800 donations, raising almost Rmb30,000 — enough for one course of treatment with the drug Myozyme, manufactured by French company Ms Li was unable to gain any state reimbursement for the drug.

People trying to pay for a treatment for a rare disease in China face bills that are on average three times their annual individual incomes and nearly two times higher than their household incomes, according to a survey of rare disease sufferers carried out in 2015.

There are about 35,000 Pompe patients in China, according to an association representing sufferers. About 80 per cent of them are adults who face annual medical costs of around Rmb3m compared with annual average incomes in China of about Rmb70,000 a year. It is impossible for sufferers in most parts of China to obtain government insurance contributions for Pompe drugs.

Ji Chongzhe, of Jilin province in the north-east, says his child developed Pompe symptoms at seven months, but local doctors initially thought it was a cold. Only after a genetic test at a hospital in Beijing was the disease identified. Eight hospital stays later, Mr Ji says he has spent his life savings — over Rmb100,000 — on treatment. He earns just Rmb4,000 a month. "After the New

Expensive burden: there is scant health coverage for diseases such as epidermolysis bullosa (above) — Shanghai Butterfly Centre

genetic disorder that can cause a

Huang Rufang, founder of the

drugs to Chinese patients", says Krishna

Healthcare How it works in China

Basic healthcare coverage was free for Chinese citizens until the 1980s, after which state-run hospitals began to charge for treatments. China began rolling out universal state-subsidised health insurance around a decade ago. Contributions are means-tested, meaning lower earners pay less. Now, 95 per cent of the population is covered by schemes under which the state will fund part of the cost of medical treatment, compared with 30 per cent in 2012.

However, while state medical coverage in China is broad, it remains shallow. Apart from a few hundred drugs deemed essential, the only treatments eligible for state co-payment are those named on a national drug reimbursement list, which was updated last year to include about 2,500 drugs.

Many life-saving drugs, including most used to treat rare diseases, are not on this list — and their prices are set by manufacturers following the abolition of official

Sanofi.

But with thousands of other people vying for money on the platform, the final amount fell short of her Rmb300,000 target. "The second round of fundraising did not come in time," Ms Li said.

Ms Li's daughter, Yuxin, was nine months old when she died of Pompe disease, a genetic disorder which causes sugar molecules to build up in muscle tissue including the heart.

China has the world's largest population of people with rare diseases — numbering between 15m and 20m according to estimates. China has rolled out state medical insurance for some drugs over the past decade but the vast majority of orphan drugs are not included. Even when they are, there is no guarantee that regional insurers will cover them. Myozyme, a treatment for Pompe, was approved for use in China in 2015 but

Year holiday we will sell our house, but that will only keep us going for half a year. After that if there's still no medical coverage, we can only wait for death."

Medhat El-Bialy, head of rare diseases in emerging markets at Sanofi, admits

'Solving the payment problem in China is much tougher than solving the approvals problem'

limited insurance is a key barrier to access. With only 38 per cent of orphan drugs available in the US on the market in China "there is catching up to do," he says.

Wang Cheng's four-year-old daughter suffers from Gaucher's disease, a rare build-up of fatty substances in certain organs. He estimates that of the approximately 400 people in the country with the condition, 138 have received help from charity programmes while at least 100 patients have no access to medicine at all. Efforts to treat the disease severely strain charity budgets. Treating just six Gaucher's disease patients in Shanghai costs the Shanghai Rare Disease Prevention and Treatment Fund about Rmb2m a month, according to its chairman Li Dingguo.

Access to healthcare can also depend on residency. Zhou Yingchun's family has just paid Rmb300,000 for a bone-marrow transplant for their 15-year-old daughter who suffers from epidermolysis bullosa — a condition which causes the skin to blister and tear. As the operation was performed outside the family's official place of residence, the family had to pay the entire cost themselves.

Chinese Organisation for Rare Disorders, says wider government insurance was the most urgent need for rare disease patients. "Overall the provincial insurers do not do a good job," he says.

But recent moves by policymakers give some hope. Beijing last year announced it would draw up its first official list of rare diseases which could open the door for wider cost support.

Some wealthier provinces have already added rare disease drugs to their reimbursement lists, he adds, while the China Food and Drug Administration, the top pharmaceutical administrator, has vowed to speed up the process for approving new treatments. "I think the CFDA's measures have encouraged drug developers," Mr Huang says.

The drug administrator's move "creates an opportunity for Pfizer and for other companies to bring innovative

Padmanabhan head of rare disease marketing in China for the US company, describing a "huge unmet medical need" in the country.

Chinese companies are also spotting the opportunities. Beijing-based start-up Prosit Sole Biotechnology is developing a treatment for norovirus gastroenteritis in immunocompromised patients, a market it estimates could be worth $500m per year in the US although only half of that amount in China.

The group intends to run trials in the US, a sign of its overseas ambitions. "Getting insurance coverage in China for orphan drugs is very tough, whereas the system in the US and Europe is more mature. That's why we are focusing on overseas markets," says Prosit's founder Liu Hongyu. "Solving the payment problem in China is much tougher than solving the approvals problem."

price caps for most drugs in 2015.

Provinces determine the level at which most drugs on the national list are reimbursed, depending on their resources. As a result, the proportion of costs paid by the state can be as low as 30 per cent. Patients generally pay a larger proportion of their medical bills in China's poorest provinces and in the countryside, even though incomes are also generally lower.

A rare disease charity in China says the typical annual cost of Myozyme, which is used to treat Pompe disease, is Rmb2m ($315,000). Most provinces will not contribute towards the cost of the drug, which means patients or their families will have to fund the entire cost themselves.

Tom Hancock and Wang Xueqiao