SNAPSHOTS

Cross-modal learning
In a study published in *eNeuro*, adult mice were made to spend a week in darkness. When tested, the brains were found to have been rewired. Their hearing sensitivity was altered long after the optimal window for auditory learning passed. Such a manipulation of one sense to help another (cross-modal learning) could be used in future to help people with disabilities. More studies are needed.

Hot rocks
Greenhouse gas emissions from the movement of volcanic rocks can create massive global warming effects, according to a paper in *Nature Communications*. The researchers noted the role of Large Igneous Provinces (extremely large accumulations of rocks forming when magma travelled through the crust towards the surface) in climate change through the Mesozoic.

A typhoid vaccine manufactured in India offers 82% protection

Unlike other two vaccines, the tested vaccine can be given to babies who are just six months old

R. PRASAD

A typhoid vaccine (Typbar TCV) developed by the Hyderabad-based Bharat Biotech has shown 81.6% efficacy in preventing typhoid fever at 12 months in a phase-3 clinical trial. The trial was carried out in Nepal in over 10,000 children who received the vaccine.

A single dose of the vaccine was found to be effective in preventing typhoid in children aged nine months to 16 years. The vaccine confers protection two-three weeks after vaccination. The duration of protection is currently not known. The results of the trial were published in *The New England Journal of Medicine (NEJM)*. The Typbar TCV vaccine was recommended by WHO's Strategic Advisory Group of Experts on Immunization (WHO-SAGE) in December 2017. The WHO prequalified the vaccine in January 2018.

Typhoid fever is caused by highly contagious *Salmonella* Typhi bacteria. Nearly 11 million fall sick due to typhoid and about 1,17,000 deaths are reported each year. The bacteria spread through contaminated food and water.

Efficacious: A single dose of the vaccine was found to be effective in preventing typhoid in children of ages between nine months and 16 years.

Key advantages

The Typbar TCV typhoid vaccine tested in Nepal is a conjugate vaccine. A conjugate vaccine is one in which the antigen (which is a polysaccharide in this case) is chemically linked to a carrier protein.

Two other typhoid vaccines – polysaccharide typhoid vaccine and live, weakened typhoid vaccine – are already used commercially. But the efficacy of these vaccines to protect against typhoid is lower than the conjugate vaccine that has now been tested in Nepal.

"The other two vaccines offer 60-70% protection unlike the conjugate vaccine which confers nearly 82% protection. Two doses of live, weakened typhoid vaccine are needed to reach 60-70% protection," says V. Krishna Mohan, Executive Director at Bharat Biotech. "More importantly, the conjugate vaccine can be given to babies as young as six months, while the other two vaccines cannot be given to children below two years of age." According to SAGE, in high-incidence settings, a large proportion of severe typhoid fever cases occur in children aged below two years.

While typhoid bacteria can be treated with antibiotics, the microbes have developed resistance against multiple antibiotics. Multidrug-resistant typhoid bacteria are seen in south Asia including India. Since 2016, extensively drug-resistant (XDR) typhoid outbreaks have been reported from Sindh province in Pakistan. According to an editorial accompanying the paper, XDR typhoid has been found in India, Bangladesh, and Pakistan.

Earlier trials

Earlier, a small phase-3 trial carried out in India by Bharat Biotech and University of Maryland School of Medicine, Baltimore, in two groups – 2-45 years old and 6-23 months old – found that a single dose of the vaccine was able to provoke immune response in 98% of the vaccinated children. The results were published in the journal *Clinical Infectious Diseases*.

A phase-2b human challenge trial was carried out in adult healthy volunteers aged 18-60 years who are typhoid naïve (no history of typhoid infection or vaccination). The volunteers were first vaccinated and then exposed to the bacteria to assess the ability of the vaccine to prevent infection. The results published in December 2017 in *The Lancet* showed that the vaccine has 88% efficacy in preventing an infection.

Exported to Pakistan

The vaccine has already been licensed in India and is available for clinical use. The company has been supplying the typhoid conjugate vaccine to Pakistan since 2017. "So far about 10 million vaccines have been supplied to Pakistan," says Dr. Mohan. Pakistan is the first country to introduce the typhoid conjugate vaccine as part of its national immunisation programme.

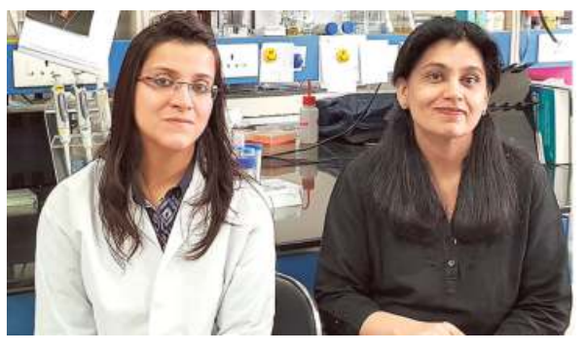
Novel molecule to combat multidrug-resistant bacteria

The molecule identified by IIT Roorkee kills the bacteria by damaging the DNA and by inhibiting cell division

R. PRASAD

Screening a small-molecule library of about 11,000 compounds, researchers at the Indian Institute of Technology (IIT) Roorkee identified a potent molecule that exhibits broadspectrum bactericidal activity against multidrug-resistant bacteria – *Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae* and *Mycobacterium tuberculosis*. The molecule also shows antibacterial activity against *Staphylococcus aureus* and diarrhoea causing *Clostridium difficile*.

In mice infected with sepsis-causing bacteria *A. baumannii,* the molecule was found to significantly reduce the bacterial load in the spleen, lungs, kidney and liver at half the dose of a well known drug nitrofurantoin. The results were published in *Journal of Antimicrobial Chemotherapy*.



Potential drug: The molecule was more effective in killing *E. coli* than nitrofurantoin, say Ranjana Pathania (right) and Timsy Bhando.

> **Since the molecule targets two pathways to kill the bacteria, microbes are less prone to resistance generation or would take a longer time to develop resistance.**
>
> RANJANA PATHANIA
> IIT Roorkee

Nitrofuran class

The molecule belongs to the nitrofuran class of antibiotics – nitrofurantoin and furazolidone – which are routinely used for treating urinary tract infections and intestinal ailments, respectively.

The team led by Ranjana Pathania from the Department of Biotechnology at IIT Roorkee found that the molecule kills the bacteria by damaging their DNA as well as by inhibiting cell division. When half the concentration required to kill the bacteria was used, the researchers found the daughter cells were unable to separate on cell division, leading to the bacteria forming into long filaments. "Since the molecule targets two pathways to kill the bacteria, microbes are less prone to resistance generation or would take a longer time to develop resistance," says Prof. Pathania.

"Even at 16-fold less concentration, the molecule was more effective in killing *E. coli* compared with nitrofurantoin," she says. The molecule was found to be effective against both gram-negative and Gram-positive bacteria as well as against anaerobic bacteria such as *C. dificile*. Compared with nitrofurantoin and furazolidone drugs, the molecule was able to kill anaerobic bacteria at many times lower concentration.

The team generated mutants to the molecule and ascertained that the molecule was a pro-drug like the rest of the nitrofuran class of antibiotics. Bacteria are less likely to develop resistance against a pro-drug as it becomes active only after getting inside the bacteria. The active components formed from the pro-drug are potent and short-lived, thus not giving the bacteria sufficient time to develop resistance.

Persister bacteria

Besides killing actively dividing bacteria, the molecule was effective against persister bacteria that remain in a dormant state. Persister bacteria can survive high doses of antibiotic treatment and are responsible for causing recurring bacterial infections. The researchers generated *E. coli* persisters and tested the ability of the molecule to kill them using two, four and eight times the minimum dosage required to kill the bacteria. "By the end of 12 hours, there's a significant reduction in the persisters at four and eight times the MIC," says Timsy Bhando from IIT Roorkee and the first author. "Pro-drug does not differentiate between dormant and metabolically active bacteria and so they get into even the dormant bacteria. The molecule then kills the dormant bacteria by damaging the DNA."

Doubly effective

Not only was the molecule able to inhibit biofilm formation (which helps bacteria to protect themselves from the action of antibiotics), but was also effective in disrupting the already formed biofilms. Compared with the molecule, both nitrofurantoin and furazolidone drugs displayed "poor ability" to eradicate already formed biofilms.

Bacteria generally can tolerate antibiotics by flushing out the drugs using the efflux pumps. "Even when we shut down the efflux pumps using an inhibitor, the amount of molecule required to kill the bacteria did not reduce much. So the efflux pumps are ineffective in pushing out the molecule from the inside the bacteria," says Dr. Bhando.

Generally, reactive oxygen species (ROS) generated by a drug helps kill the bacteria. But in the case of the molecule identified by the team, generation of the reactive oxygen species followed bacterial killing. To ascertain if ROS generation killed the bacteria or was produced after the death of the bacteria, the researchers pre-treated *E. coli* with vitamin C, an antioxidant that removes the ROS. "Even after pre-treatment with vitamin C, bacteria were dying. So ROS is a consequence of DNA damage and was not the cause of bacteria death," Pathania says. The study was done in collaboration with Government Medical College and Hospital, Chandigarh, AIIMS, Bhopal and AIIMS, Delhi.

Bats may be well adapted to forest fires

PRESS TRUST OF INDIA

Bats may be well adapted to wildfire, according to a study which surveyed the effects of burn severity of 17 species of the flying mammal in forests that experienced fires.

The researchers, including those from the University of California (UC) Davis in the US, said while many forest bats are adapted to dense spaces, and others with open habitats, they found that species from both groups preferred burned forests to unburned or minimally burned forests.

To understand how wildfire was affecting bat habitat, they used an acoustic surveying technology with microphones that emitted very high frequency sound, and tracked patterns in the way bats communicated.

The recordings were converted into visualisations of bat calls, using which the scientists could identify the species present, and compare their occurrence rates to habitat conditions.

The study, published in the journal *Scientific Reports,* noted that while individual species responded to wildfire differently, the overall richness of bats increased from about eight species in unburned forests to 11 in forests that experienced moderate- to high-severity burns. This seems to suggest that many bat species seem to benefit from fire.

2.3 million children in India unvaccinated for measles

India is second highest, next only to Nigeria with 2.4 million

SPECIAL CORRESPONDENT

In 2018, measles caused an estimated 10 million cases and 1,42,000 deaths globally, according to a report published on December 6. The estimated cases and deaths are much more than what countries have reported to the World Health Organization and UNICEF. The number of measles cases reported in 2018 was only 3,53,000.

Children at risk: In 2017, 2.9 million children in India under one year of age were not vaccinated. ▪ M. PERIASAMY

Preventable condition

Measles can be prevented through two doses of vaccination. But the number of children who are not vaccinated against measles is alarmingly high in six countries. At 2.3 million, India has the second highest number of children who are not vaccinated against measles, the report published in *Morbidity and Mortality Weekly Report* (MMWR) says. With 2.4 million, Nigeria has the most number of unvaccinated children. The other four countries with the most number of unvaccinated children are Pakistan (1.4 million), Ethiopia (1.3 million), Indonesia (1.2 million) and the Philippines (0.7 million).

In 2017, 2.9 million children in India under one year of age had not been vaccinated with the first dose, according to UNICEF. In one year, the number of unvaccinated children in India had reduced from 2.9 million to 2.3 million. The corresponding reduction in the case of Nigeria has been much more – from nearly 4 million unvaccinated children in 2017 to 2.4 million in 2018.

There were nearly 70,000 cases of measles in India in 2018, the third highest in the world. In 2019, over 29,000 confirmed cases have been reported to the WHO.

The WHO recommends 95% coverage using two doses of measles vaccine to prevent outbreaks. Though vaccine coverage with first and second dose has increased globally since 2000, it has not reached anywhere near 95%. In 2018, only 86% of children globally received the first dose through routine immunisation. In the case of second dose, the coverage globally is just 69%.

Failing to immunise

In India, the first dose of measles vaccine is given at nine-12 months of age and the second dose is given at 16-24 months of age through the national immunisation programme. But it appears that millions of children in India do not receive measles vaccine through routine immunisation activities.

According to the MMWR report, in 2018, 19.2 million children globally worldwide did not receive the first dose through routine immunisation services. Nearly 163 million children in India received the measles vaccination during mass immunisation campaigns. India accounted for 47% of the 346 million children across the world who received measles vaccine during mass-immunisation campaigns.

Effective strategy

Mass immunisation campaigns are an effective strategy for delivering vaccination to children who have otherwise been missed by routine services. But it does reflect how many children get missed by the routine immunisation programme.

The first dose of measles vaccine was introduced as part of the national immunisation programme in the 1990s. Based on the WHO's recommendation to administer a second dose to prevent infection and death in 90-95% of vaccinated children, India introduced the second dose from 2010 onwards. India was one of the last countries to add a second dose of measles vaccine as recommended by the WHO.

The first mass immunisation campaigns for the second dose of measles vaccine were launched in 2010 in 14 States where the coverage for the first dose was below 80%. The campaign targeted children aged nine months to 10 years of age.

Brewing interest: Coffee is arguably one of the most studied components of our diet. ▪ K. PICHUMANI

Coffee is a health drink, but do not overdo it

Most south Indians drink a mixture of coffee and chicory

SPEAKING OF SCIENCE

D. BALASUBRAMANIAN

It is well known that black tea (that we Indians drink) is a health drink. A concise summary by Dr. A. Enloe on its ten major benefit appears in *Heathline,* May 16, 2018 issue. A similar analysis on coffee as a health drink appears in the November 28, 2019 issue of *Specialty Medical Dialogues,* Dr. Hina Zahid writes: "Coffee is arguably one of the most studied components of our diet, with an extensive range of research published in areas of mental performance, sports performance, fluid balance, type 2 diabetes, liver function, neurodegenerative disorders, pregnancy, cancer, and cardiovascular disease (CVD). Metabolic syndrome is a condition which is estimated to affect more than one billion people across the globe and it increases the risk of cardiovascular problems, including coronary heart disease and stroke. A report from the Institute for Scientific Information on Coffee (ISIC) highlights the potential role of coffee consumption in reducing the risk of developing metabolic syndrome and states:"The new report of meta-analysis has suggested that drinking 1-4 cups of coffee per day is associated with a reduced risk of metabolic syndrome in observational studies."

A meta-analysis combines the results of many scientific studies addressing the same question, analyses the result of all these, identifies how well they lead to the same conclusion, and to what level they may differ from one another. It thus offers a more robust summary of the main conclusion and the acceptable "take home message". Dr. Guiseppe Grosso and colleagues of the Catania University, Italy conclude that coffee consumption reduces the risk of type 2 diabetes, hypertension and so forth (see Grosso et al;. *Annual Review of Nutrition* 2017, 37; 131-156). Another meta-analysis by Navarro et al; *Clinical Nutrition* 2019 Feb.,38 (1): 389-397 shows that regular consumption of coffee helps in reducing the risk of hypertension.

People who are interested in finding out more about coffee and health may visit http://www.coffeeandhealth.org, which offers a detailed analysis on the benefits of coffee on health. These all suggest that coffee is a health drink, but in small amounts (3-5 cups day) Drinking too much of it is also bad. Mayo Clinic advises that going beyond this is an overdose, and that the increased caffeine levels lead to migraine headache, insomnia, restlessness, muscle tremors, and fast heartbeats. It is thus wise to limit the cups. Also, it should not be given to children. Pregnant mothers may further restrict their cups.

Arrival in India

Coffee, originally Ethiopian in origin, was quickly taken over and held tight by the Arabs as their own drink (since wine was prohibited) that alerts the imams and the believers. The "Insight" column of http://madrascouriers.com of June 19, 2017 states that the 16th century Sufi saint Baba Budan smuggled several seeds of it from the Arab monopoly, and planted them in Chikkamagalur of the Mysore kingdom in 1670. Although, it might have been brought to the Malabar Coast earlier by Arab traders. It is thus that coffee was planted and grown in Karnataka, Kerala and Tamilnadu. Recently, it is also grown in the Araku Valley of Andhra Pradesh and more recently in some of the 'seven sisters' states of northeast India , And this also appears how coffee drinking seems to have become a popular daily drink in Peninsular India since centuries.

But then most south Indians drink not pure coffee, but a mixture of coffee and chicory. Chicory, a native plant, is cultivated and grown the in the Mediterranean regions of Spain, Greece, and Turkey. It became popular in Europe both on its own and as an addition to coffee. The site "Bynemara Tales-Medium" points out in its 19-7-2017 issue that France started using it due to the shortage of coffee there in the early 1880s. Since then the coffee-chicory duo became popular. The English writer Charles Dickens (of 'David Copperfield' and 'A Tale of Two Cities' fame) is said to have written: "By the combination of a little chicory with coffee, the flavour of the coffee is not destroyed, but there is added to the infusion a richness of flavour, and a depth of colour - a body- which renders it to very many people much more than welcome as a beverage". And that the colonial British played a key role by introducing what they called as "camp coffee", a secret blend of water, sugar, 4 % caffeine-free coffee essence and 26% chicory essence. And Indian soldiers and people at large warmed up to it. Over time, South Indian coffee has come to mean a mixture of coffee and chicory in varied ratios, anywhere from 80% coffee and 20% chicory powder to the more common 60-40 ratio. We also cultivate chicory in India - in Gujarat and UP, where the soil and the climate suits it best.

Going beyond south India

Traditionally, the South Indian Coffee confined itself to the four southern states, while tea was more popular and widely drunk almost exclusively in the North, since they produced, harvested and marketed the tea plant and its leaves in Assam, West Bengal and some of the northeastern states, where the climatic and soil conditions suit the plant best. But in recent times, more 'Southies' have also taken to tea, not as an alternative, but additionally. And the 'Northies' to coffee, again additionally. A major reason behind this has been marketing. Even here, apart from 'filter coffee', we now have other genre such as espresso, cappuccino, and such Western introductions, particularly among the city dwellers. What used to be *'chai pe charcha',* where all kinds of debates, discussions and meeting (or not) of minds, and new political ideas used to occur over tea, which Satyajit Ray epitomised in his film Agantuk, we have now added coffee shops (with free wi-fi connectivity) which are advertised as "a lot can happen over coffee". But they are not the same as the *addas* of yesteryears.

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