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BCG REVACCINATION STUDY IN HIGH-RISK ADULTS TO BEGIN IN 23 STATES

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

December 02, 2023 09:00 pm | Updated 09:00 pm IST

Twenty-three States have consented to participate in the BCG revaccination study in adults that will be undertaken in a “programme implementation study mode” to evaluate the effectiveness of the vaccine in reducing TB disease incidence. The study will target some high-risk groups — those older than 50 years, prior TB disease, underweight adults, diabetics, and those who smoke and consume alcohol. The phase-1 of the study will be conducted in Uttar Pradesh and Madhya Pradesh, says a Delhi-based official.

No clinical trials have been carried out in India to study the efficacy of BCG revaccination in adults to prevent TB disease, and studies in other countries have thrown up mixed results. Two clinical investigation studies (2019 and 2023) by St. John’s Research Institute, Bengaluru have found BCG revaccination in adults to be significantly immunogenic.

Despite the recommendation of an expert committee that a clinical trial be carried out first, the government has decided to go ahead with the programme implementation study. “An expert committee constituted by ICMR recommended that a robust trial be carried out in India and implementation at population-level be undertaken once evidence of efficacy was available,” says Dr. Soumya Swaminathan, former Chief Scientist at WHO and a member of the expert committee. “Most studies of BCG revaccination globally have not found major impacts on reducing TB incidence. Therefore, it is not recommended by the WHO currently. However, a recent phase-2 trial in South Africa suggested it may prevent TB infection. Hence, further trials are warranted to assess the effectiveness of BCG revaccination in different populations, age groups, by timing of revaccination and types of TB.”

Since the government felt that a trial would take too long to complete and wanted to implement BCG revaccination at scale, the committee had suggested that some districts be used as an intervention arm and some as the control arm, and TB incidence be captured over a couple of years. Accordingly, 50% of the districts in a State will be included in the intervention arm and the remaining 50% will act as control.

“WHO does not currently recommend programmatic or pilot BCG revaccination [even in high-burden countries such as India],” Dr. Birgitte Giersing, Team Lead - vaccine platforms & prioritization, WHO, says in an email to *The Hindu*. The 2018 BCG vaccine position paper by WHO does not advocate BCG revaccination in adults. It says: “Studies have shown minimal or no evidence of any additional benefit of repeat BCG vaccination against TB or leprosy.

Therefore, revaccination is not recommended."

The protective effect of a single dose of the vaccine given to infants in India wanes within a short time. A 15-year follow-up study found that at the end of 7.5 years there was "complete lack of protective efficacy" in children. Even if revaccination offers protection in adults, the duration of protection remains to be seen.

Incidentally, while NIRT in Chennai will be conducting a BCG booster dose clinical trial in children aged 6-18 years, the BCG revaccination study in adults is being undertaken mainly based on the retrospective data analysis of a small sub-group of the Chingleput BCG vaccination trial conducted in 1968. In the 1968 trial, 2,890 adults received a BCG revaccination and 1,546 did not, and the efficacy of the vaccine to reduce TB incidence was found to be 36%. But the protective efficacy was seen only at the end of 15 years of follow-up, and the protective effect of BCG revaccination was significant only in the 31-40 years age group.

The Chingleput BCG revaccination study has several limitations — the sample size is small, potential confounders such as nutritional status, diabetes, smoking and alcohol consumption, and TB exposure status are not known, and the time interval between the first dose and BCG revaccination is also not known.

"We could carry out a 'phase 3'-like randomised controlled trial, or we could carry out a 'phase 4'-like ('pilot') pragmatic evaluation of the roll-out of the vaccine. As BCG is an already-licensed vaccine… the effectiveness information India (and the world) needs on whether BCG revaccination prevents TB disease could be gained from a phase 4-like ('pilot') study as long as it is done well enough," Dr. Richard White, Professor of infectious disease modelling at the London School of Hygiene & Tropical Medicine says in an email.

Tamil Nadu, which has consented to participate in the study, has 44 TB districts. Half of these will be earmarked as intervention arm and the remaining as control. "Since adults belonging to high-risk groups are to be studied, the number of consenting participants will run into lakhs," says Dr. T.S. Selvavinayagam, Director of Public Health and Preventive Medicine, Chennai. "The safety profile of BCG revaccination will be studied programmatically, while a sub-group of participants running to a few thousands will be followed-up for two-three years by NIRT for vaccine efficacy." The study will begin in Tamil Nadu once the State government approves it.

Kerala, Bihar, Chhattisgarh, West Bengal and Uttarakhand that have not consented to participate in the study. "The field constraints to carry out the study is the only reason why Kerala did not consent to participate," a Kerala official says. "The staff involved in the universal immunisation programme will be overburdened when BCG revaccination is included. There are gaps in the immunisation programme in Kerala after the pandemic. The focus is on closing this gap. So Kerala did not want to begin the BCG revaccination programme now."

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Source : www.thehindu.com Date : 2023-12-09

INDIA’S ALARMING ‘FIXED DOSE COMBINATION’ PROBLEM

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

December 09, 2023 12:16 am | Updated 08:08 am IST

‘The FDC problem has been on the regulatory radar since 1978’ | Photo Credit: Getty Images

A group of academics from India, Qatar and the United Kingdom recently published a worrying new study in the Journal of Pharmaceutical Policy and Practice (2023, 16:39) on the volume of unapproved and even banned fixed dose combination (FDC) of antibiotics that are being sold in India. Using sales data of the pharmaceutical industry, the study documents that in the year 2020, 60.5% FDCs of antibiotics (comprising 239 formulations) were unapproved and another 9.9% (comprising 39 formulations) were being sold despite being banned in the country. That so many of these unapproved or banned FDCs contain antibiotics is alarming because of the increasing prevalence of antibacterial microbial resistance (AMR) in India.

FDCs are combinations of one or more known drugs and can be useful in the treatment of some diseases since the combination can improve patient compliance. For instance, if a patient has to take three different medications for a particular treatment, she may forget to take one. But if all three medications are combined into one tablet or one syrup, the chance of her forgetting to take one or two of the drugs is reduced. For diseases such as AIDS, it is well documented that FDCs have proven to be very useful in improving patient compliance, which at the end of day improves treatment outcomes.

Making FDCs, even though most consist of drugs with known safety and efficacy profile, is not an easy job. All drugs have side effects and when formulated together, there is a possibility that the active ingredient or even the excipients (inactive ingredients) may affect the way that each drug functions. For example, the drugs may interact in a way to reduce the therapeutic efficacy of each active ingredient, or, worse, the drugs may interact with each other to create a more toxic element, often called metabolites. This is why it is crucial that all FDCs go through a scientifically designed approval process where such interactions can be evaluated.

Pharmaceutical companies in India use these FDCs to escape liability under multiple laws without much concern for public health. One such law is the Drugs (Prices Control) Order (DPCO), under which the government fixes the prices of individual drugs. Since drug combinations were traditionally not covered under the DPCO, the pharmaceutical industry decided that making FDCs provided an easy way to escape the remit of the DPCO.

Also read |Manufacture and sale of 344 FDC drugs banned

Driven by this cold logic of the market, and not public health, the Indian pharmaceutical industry introduced an astounding variety of FDCs that lacked any medical rationale. For example, anti-inflammatory drugs were combined with vitamins, anti-histamines were combined with anti-diarrhoeal agents, penicillin was combined with sulphonamides, and vitamins were combined with analgesics. These were combinations not found in any other country.

There were two added advantages of adopting this strategy for the industry. The first, the fact that because of the bewildering variety of FDCs being sold in the market, there were no standards set by bodies such as the Indian Pharmacopoeia Commission for testing these drugs for quality of manufacture. When there are no standards recognised by the law, there is no question of manufacturing “not of standard quality” drugs, and hence there is no possibility of prosecution under the Drugs & Cosmetics Act, 1940. At most, when these FDCs are sampled in the market and sent for testing, the usual protocol for government laboratories conducting such tests is to write to the manufacturer and ask for their own protocols to test the drug. In other words, the pharmaceutical industry gets to provide its own standards in order for the government to test their drugs.

The second advantage of going down the FDC route is that it gives individual companies a reason to charge higher prices for their drugs. For example, if 20 different pharmaceutical companies were manufacturing and selling a drug such as azithromycin, they would have to compete furiously and reduce prices to capture a larger share of the market. But if they combine azithromycin with another drug, for example, cefixime to create a FDC, they can claim it as a new unique product catering to a specific need, thereby allowing them to charge a higher price until others introduce similar products, at which point the first mover may try to create a new FDC. When the market and the regulatory structure rewards these manufacturers of such pseudo-innovation rather than for discovering and developing true innovative medicines, this is what happens. These dubious FDCs can command higher prices. Of course, none of this is possible without doctors who are willing to prescribe such FDCs. While it is tempting to paint all such doctors as corrupt, the fact of the matter is that most doctors wrongly presume that the drug regulator is doing its job when a product is sold on the market.

The FDC problem has been on the regulatory radar since 1978 when the first government committee studied the issue and admitted that we had a problem on our hands. At the time, there was no system under the colonial-era Drugs and Cosmetics Act, 1940 to vet drugs for safety and efficacy prior to their sale in India. This meant that each State drug controller could hand out manufacturing licences for any drug formulation and there was little that the central government could do to stop their sale.

In 1982, Parliament changed the law to give the central government the power to “prohibit” the manufacture of specific drugs that lack therapeutic value or justification. Later in that decade, in 1988, the central government amended the rules to introduce a new requirement for manufacturers of all “new drugs”, including FDCs, to submit proof of safety and efficacy to the Drugs Controller General of India (DCGI) who heads the Central Drugs Standard Control Organization (CDSCO). These amendments also made it clear that State drug controllers could not grant “manufacturing licences” for “new drugs” that are not approved for safety and efficacy by the DCGI.

Despite the law being crystal clear on the issue, State drug controllers have simply ignored the law to continue issuing manufacturing licences for FDCs not approved by the DCGI with impunity. The manufacturers selling these FDCs that have not been approved by the DCGI can technically be prosecuted by the Central government for violating the law.

Instead of ordering criminal prosecutions, the Ministry of Health is playing a game of whack-a-

mole by constantly invoking its powers under Section 26A to prohibit the manufacture of specific FDCs. It has issued 444 orders under this provision since 1983, banning mostly FDCs. Many of these orders have been embroiled in complex litigation, with the courts muddying the waters with inconsistent decisions.

Also read | National Medical Commission lists drugs which can be sold without prescription

The fact that these academics have discovered 239 unapproved FDCs being sold in 2020 in just one category of FDCs (their previous studies have revealed similar unapproved FDCs in other therapeutic categories), more than 42 years after the problem was first flagged is an astonishing indictment of the incompetence of the drug regulatory framework in India. As they point out in their paper, unregulated FDCs may end up contributing to the AMR problem in India. It is vital for the Ministry of Health to take immediate action.

Dinesh S. Thakur and Prashant Reddy T. are the co-authors of* The Truth Pill: The Myth of Drug Regulation in India *(2022)

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PROTEIN FROM BUDGETT'S FROG CAN BLOCK ENZYMES OF DISEASE-CAUSING PATHOGENS: STUDY

Relevant for: Science & Technology | Topic: Science and Technology- developments and their applications and effects in everyday life

December 10, 2023 10:39 pm | Updated December 11, 2023 02:19 am IST - Bengaluru:

According to researchers, frogs have developed a defensive mechanism through their skin, which helps to combat microorganisms.

Researchers from the Indian Institute of Science's (IISc.) molecular biophysics unit in a study have identified that peptides (short protein) produced from Budgett's frog can combat enzymes of disease causing pathogens

According to IISc., peptides (short proteins) produced from the skin of amphibians have long been studied because of their ability to counter unfavourable conditions in the environment, including harmful pathogens.

Mihir Rami, Mohd. Shafique, and Siddhartha Sarma at the unit have studied LL-TIL, one such peptide found in skin secretions of Budgett's frog.

According to Mr. Rami, Budgett's frog found in South America is kept as a pet in many countries because of their intelligent behaviour.

"Frogs are the first vertebrates to conquer the land and all other vertebrates like reptiles, mammals, and birds came after the amphibians. Because of this the frogs have developed a defensive mechanism through their skin. They generally combat the microorganisms and other harmful things through their skins," said Mr. Rami.

The IISc. said that the researchers found that the frog-secreted peptide inhibited two key enzymes called subtilisin carlsberg and proteinase K., produced by pathogens.

"These enzymes play a pivotal role in promoting infections by degrading specific protective proteins of the infected person. The team used various spectroscopic techniques and protein assays to study the binding of the amphibian peptide to the pathogenic enzymes. The peptide was shown to act through a slow-tight binding pathway, and was found to be as effective as SSI, a well-known subtilisin inhibitor," said IISc.

The study further revealed an in-depth mechanism of this inhibitory action, using structural and

dynamic models. The researchers show the formation of a Michaelis complex – a tight, noncovalent complex with the intact inhibitor – during the process. They also studied the effects of modifications to the original sequence of the peptide.

“This provides a framework to engineer more specific and potent TIL-type inhibitors, which can be used against other pathogenic enzymes as well,” IISc. said.

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Source : www.thehindu.com Date : 2023-12-13

GAME-CHANGER: THE HINDU EDITORIAL ON APPROVAL FOR GENE THERAPY TO TREAT SICKLE CELL DISEASE AND BETA THALASSEMIA

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

December 13, 2023 12:10 am | Updated 12:10 am IST

Less than a month after the U.K. drug regulator approved Casgevy, the gene therapy to treat people above 12 with sickle cell disease and beta thalassemia, the U.S. FDA has approved two gene therapies — Casgevy and Lyfgenia — to treat sickle cell disease in patients over 12. Its decision on approving Casgevy gene therapy for treating beta thalassemia is expected by March 2024. These landmark decisions mark the beginning of gene therapy using the CRISPR-Cas9 tool to treat diseases that could otherwise be cured only through bone marrow transplantation. While Lyfgenia uses a disabled lentivirus as a vector to introduce into the blood stem cells a new gene for haemoglobin that mimics the healthy version, Casgevy uses the gene-editing tool of CRISPR-Cas9 to disable a particular gene (BCL11A) that turns off foetal haemoglobin production in blood stem cells. While about 10% of adults continue to produce foetal haemoglobin, in others, the BCL11A gene prevents the production of foetal haemoglobin. By disabling the BCL11A gene, foetal haemoglobin that is produced, which does not have the abnormalities of adult haemoglobin, helps treat patients with sickle-cell disease or beta thalassaemia. In clinical trials, 28 of 29 sickle-cell disease patients who received Casgevy gene therapy were relieved of the debilitating effects of the disease for a year; for beta thalassaemia, 39 of 42 patients did not require blood transfusion for one year, and in the remaining three the need for blood transfusion reduced by more than 70%. In the case of clinical trials involving Lyfgenia, 30 of 32 sickle cell disease patients did not suffer from severe blocked blood flow caused by sickle cells, while 28 of 32 patients did not experience any blocked blood flow events six to 18 months post-infusion.

Since both gene therapies use patients' own blood cells for gene editing, the number of patients who can potentially be treated will be huge as these treatments do not rely on matching bone marrow donors. But in reality, these treatments would be exorbitantly expensive. Also, much like bone marrow transplantation, only certain hospitals will be equipped to extract a patient's blood stem cells and use the genetic editing tool to the stem cells before reinjecting them, thus limiting the number of beneficiaries. With clinical trials evaluating the therapies in a very small number of patients and for shorter duration, the compulsion to continuously monitor their safety and efficacy through real world data cannot be overemphasised: the possibility of unintended genetic modifications and their resultant side effects are real when the CRISPR–Cas9 tool is used.

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