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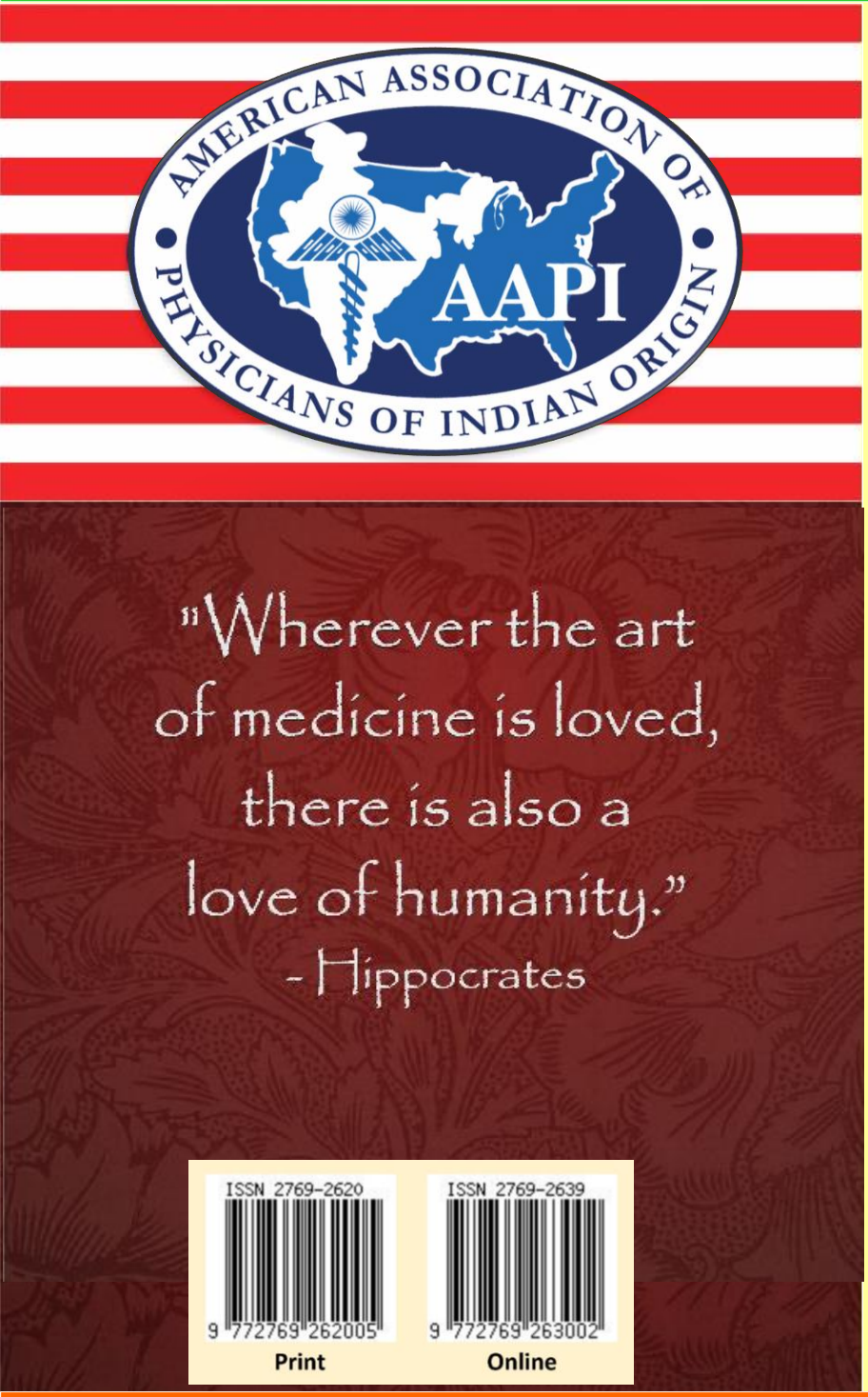

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In this Issue…

This Summer Issue of JAAPI is Dedicated to

Edward Jenner, FRS

Father of Immunization

(1749 -1823)

Physician, Surgeon, Biologist, Geologist, and Humanitarian, Who Experimented with Blood, Birds and Balloons

JAAPI: Summer Issue: September 2021 Vol 1 No. (2)

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Pioneers in Medicine and Healthcare

Edward Jenner, FRS

Father of Immunization

Physician, Surgeon, Biologist, and Humanitarian,
Who Experimented with Blood, Birds, and Balloons

In science the credit goes to the man who convinces the world, not the man to whom the idea first occurs. – Francis Galton

As the world is battling against COVID-19 pandemic, terms such as RNA vaccines, herd immunity, and mutants have become household names. But, hardly two hundred years ago the term immunization was not known to the world, when about 400,000 people were dying each year in Europe alone due to smallpox. We should credit Edward Jenner, the Father of Immunization for opening up a new field in medicine, healthcare and epidemiology. Jenner was a multifaceted genius with a very unusual track record of training and work. Born on May 17, 1749 in Berkeley, Gloucestershire, England, Edward was orphaned at 5 years, and was raised by his elder brother. In the school, Edward developed strong passion for science and nature. At 13 years, he did an apprenticeship with a country surgeon and apothecary near Bristol. It was during the apprenticeship Edward heard a dairymaid saying *I shall never have smallpox as I have had cowpox. I shall never have an ugly pockmarked face.* Later Edward went to do apprenticeship with George Harwicke and John Hunter, the famous surgeon. Both Jenner and Hunter had a natural love for biology and nature, and they worked together on those lines. Jenner also helped to classify the biological materials brought back by Captain Cook from his voyages. Jenner studied geology, and experimented with human blood. Just two years after it was invented, Jenner built his own hydrogen balloon that flew several miles. He did research on cuckoo and published a remarkable paper on this bird, for which he was elected as a Fellow of the Royal Society (FRS). He also studied hibernating hedgehogs. As a clinician and surgeon, Jenner showed innovation in his work. Besides publishing on medical topics, he used to play violin in a local club and composed poetry and light verse.

Although Jenner heard the dairymaid's words about her immunity against smallpox when he was a teenage apprentice, it was in 1796 at 47 years he actually tested the claims of the dairymaid. He found a dairymaid Sarah Nelms with fresh cowpox lesions on her hands and arms. He took pus from her lesions and inoculated James Phipps, an 8-year old boy. The boy developed mild fever, discomfort in the axilla and loss of appetite, but recovered. Six weeks later, Jenner inoculated the boy with pus from smallpox lesions. The boy did not develop the disease. Edward Jenner concluded that protection was complete. Jenner submitted a report of his experiment and observations to Royal Society. It was rejected. Two years later, after performing the study on a few more subjects, Jenner privately published a small booklet entitled *An Inquiry into the Causes and Effects of the Variolae vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cow Pox*. Jenner called the new procedure as *vaccination* based on the Latin word *vacca* for cow, and *vaccinia* for cowpox. Unfortunately, Jenner's theory was discredited, and it was met with skepticism by the medical community. Finally, in 1799 Drs. George Pearson and William Woodville supported Jenner by vaccinating their patients. By the year 1800 vaccination spread across Europe. Edward Jenner sent samples of his vaccine to Benjamin Waterhouse, a Professor of Physics at Harvard University. Waterhouse introduced the vaccination in New England, and persuaded Thomas Jefferson to try it in Virginia. Jefferson set up the National Vaccine Institute and appointed Waterhouse as its Vaccine Agent,

Finally, Jenner received worldwide recognition for his work, but he never made money out of his innovative work. Due to his intense research activities, his practice as a physician and his personal life suffered considerably. The British Parliament rewarded him with £30,000 in two installments. After retirement from his research on vaccines, Jenner settled down in the countryside as a practicing physician. On January 23, 1823 Jenner visited his last patient, a friend. The next day Jenner died of a massive stroke, thus ending a very illustrious and service-oriented life of extraordinary contributions to the humanity.

Source: Riedel S. Edward Jenner and the history of smallpox and vaccination. Proc (Bayl Univ Med Cent). 18: 21–25. 2005

Article Contributed by: Bellamkonda K. Kishore, M.D.

Invited Editorial

Physician Leadership in Times of Crisis and Transition

Susan R. Bailey, M.D.

President, American Medical Association

Physicians have been true heroes in this pandemic. They need the power of organized medicine working on their side now more than ever before. – Dr. Susan R. Bailey

COVID-19 has tested our physician community in ways we have never experienced, both here at home and abroad. My heart breaks when I read and see reports about the COVID crisis unfolding in India. It's a painful reminder that even while cities and states across the U.S. are re-opening in ways not seen since before the pandemic, that COVID-19 is still a very grave threat that must be delt with. I pray for the people of India, and I hope that the Biden administration will render whatever support and resources are necessary to turn the tide in this pandemic.

I would like to start today thanking the physicians, nurses, and other health care personnel across the country who have risen to the immense challenge of this pandemic. Your work over the past year has been extraordinary, and it has come at great personal risk to yourselves and your families. So, on behalf everyone at the AMA, thank you for all you have done.

AMA has Responded to the COVID-19 Crisis in Four Important Ways:

- By providing trusted, evidence-based resources and clear guidance to physicians on the front lines – resources which can be accessed for free on AMA's website.
- By helping physicians and practices recover from the disruption and damage of the pandemic by pushing for loans and other forms of financial assistance. . . and providing guidelines on how to safely reopen.
- By pushing at the highest levels of government to deliver necessary equipment, such as PPE, or to reduce obstacles to patient care.
- And by advocating for science-based, equitable policies on pandemic control strategies, testing and vaccine development and distribution.

With several safe and effective vaccines for COVID-19 now in wide circulation, it is crucial that our physician community works to get as many people vaccinated quickly as possible. Vaccination rates can differ markedly from state to state, even among neighboring counties. I believe this creates an opportunity for physicians to take on an active and vital role as vaccine ambassadors.

Experience has shown us that our patients place great faith in a strong, positive recommendation from their physicians, and that the information and education provided by physicians and other health care professionals results in higher rates of vaccine acceptance.

Telehealth Expansion:

Telehealth has been a lifeline for physicians and struggling practices during this pandemic, but also for patients too. Telehealth services is one of the few health care issues that has true bipartisan support in Congress, so we need to take advantage by pushing bills that support expanding telehealth to all who need it.

The AMA has created a Quick Guide to Telemedicine among a number of free resources for physicians that can be found on the AMA COVID-19 Resource Center on our website. There are no silver linings when it comes to COVID-19, but it's encouraging to see a paradigm shift toward telemedicine, which has become inevitable for so many. Some have said that telemedicine has advanced 10 years in 10 weeks because of the pandemic.

The AMA has forcefully advocated for telemedicine as an option for care amidst COVID-19. We also developed a Telehealth Implementation Playbook, which outlines a clear and efficient path to rapid, scaled implementation of audio and visual visits.

One of the most significant barriers to wider adoption of telemedicine has been restrictions on where patients can be located to receive these services under Medicare rules. With our urging, CMS has temporarily removed these restrictions, so Medicare patients can now receive telemedicine services from the comfort and privacy of their homes, no matter where those homes are located. We support this change and continue to work with Congress and policymakers at CMS to resolve outstanding issues.

AMA continues to press for the continuation of temporary telehealth provisions that enable better patient care, greater alignment of telehealth coverage and coding policies across all payers, and the continued suspension of regulatory hurdles. We continue to work with private insurers to mirror new Medicare telehealth flexibilities in the commercial markets, and call on employers with self-funded plans to do the same.

AMA Advocacy Priorities:

Stepping outside of COVID for a moment, I want to highlight a few of the AMA's Advocacy Priorities for this year, and frankly, for as long as it takes. The prior authorization requirements of insurance companies are a perfect example of the kind of burdens that not only frustrate physicians and office staff, but can negatively affect patient care.

Ninety-four percent of doctors reported care delays while waiting for health insurers to authorize necessary care, according to a 2020 AMA Survey. Nearly 80 percent of physicians say their patients have abandoned treatment due to PA struggles with insurers. These findings illustrate a critical need to streamline or eliminate low-value prior-authorization requirements to minimize delays or disruptions in care delivery. The AMA has taken a leading role in advocating for Prior Authorization reforms and convening key industry stakeholders to develop a roadmap for improving the prior authorization process.

Defending physicians from Scope of Practice Expansions is another major area of focus, especially during the pandemic as Nurse Practitioners, Physicians Assistants, Pharmacists, Optometrists and others have sought a larger role in patient care.

Since 2019, the AMA has secured over 70 state legislative victories stopping inappropriate scope expansions of nonphysicians, including bills that would have expanded the scope of practice of nurse practitioners in over 14 states. The AMA has worked with over 20 state medical associations on scope of practice legislation in 2021.

With a new Congress and a new Administration friendly to the Affordable Care Act, we believe the time is right to stabilize the ACA and build on its success. The AMA believes all Americans should have meaningful, affordable health care to improve the health of our nation.

We remain committed to protecting coverage for the 20 million Americans who acquired it through the ACA and expanding coverage for those who do not currently have it.

AMA is Committed to Fixing the Current System by:

- Expanding eligibility for premium tax credits and increase tax credit amounts for young adults.
- Stabilizing and strengthening the individual market, such as establishing a permanent reinsurance program.
- Improving the individual market risk pool, such as providing adequate funding for and expansion of outreach efforts to increase public awareness of coverage options and financial assistance available.

This Invited Editorial is based on the Distinguished Lecture delivered by Dr. Susan R. Bailey in AAPI Webinar on May 12, 2021 on the occasion of launching of the inaugural issue of JAAPI.

From the Editorial Desk

Coming together is a Beginning. Keeping together is Progress. Working together is Success. - *Henry Ford*

Bellamkonda K. Kishore, M.D., Ph.D., MBA
Editor-in-Chief of JAAPI

After driving on the ramp of Sushruta Medical News for a year, on May 12, 2021 we entered the highway when the Inaugural Issue of JAAPI was launched by Dr. Susan R. Bailey, President of the American Medical Association in a virtual event. That historic moment was recognized by the AAPI in its 39th Annual Convention and Scientific Assembly. For those of us navigating through the Editorial Board, it is just the beginning. There are several phases yet to be completed to establish JAAPI as a peer-reviewed and indexed medical and healthcare journal. We received the ISSN (International Standard Serial Numbers) for JAAPI issued by the US Library of Congress. In about a year and half or after publishing 40 articles, JAAPI will be eligible for registration with the National Library of Medicine (NLM), which is a stringent process of evaluation and vetting. If successful, articles published in JAAPI will be indexed in the PubMed, the benchmark for peer-reviewed scientific journals. PubMed is the leading database of publications operated by NCBI (National Center for Biotechnology Information), of the United States Government. JAAPI will also be registered to be indexed by other major bibliographic databases, such as SCOPUS (managed by Elsevier), EMBASE (Excerpta Medica Database), DOAJ (Directory of Open Access Journals), Ovid (Walter Kluwer Ovid Database) and BioMed Central Database. Thus, during the next three years JAAPI will be promoted in diverse ways.

The initial periodicity of publication of JAAPI will be three issues in a year – *Spring, Summer and Winter*. As the journal picks up momentum and submission of articles increases, the periodicity may change to bimonthly (one issue in every two months). This requires expansion of operational capabilities of the Editorial Board. To facilitate article submission by authors, handling by editors, and reviewing by experts, JAAPI has subscribed to a manuscript management service. We request AAPI Members and Medical and Healthcare Community to promote JAAPI by submitting articles and sharing information about JAAPI with others. JAAPI also welcomes advertisements from pharma industry, hospitals or clinical practices or non-profit and for-profit organizations that cater the needs of physician community. Details for advertisements are given in the JAAPI information pages in this issue.

Finally, in this Summer issue, we present excellent articles that are very useful to the physician community. Dr. Susan R. Bailey, President of the American Medical Association has kindly obliged our request and contributed an Invited Editorial. In addition, we have in-depth, broad and focused reviews, commentaries, and an observational study on COVID-19 in pediatric populations in India. We also have synopses of a few CME Lectures delivered at the recent AAPI Convention in Atlanta, GA. More importantly, the ANIO (American Association of Nephrologists of Indian Origin) has contributed a synopsis of ANIO Webinar on Kidney Diseases and Vascular Risk in South Asian Populations. We are thankful to ANIO Leadership for using JAAPI as a platform for their publication needs. We anticipate that other specialty societies of Indian American Physicians, such as Association of Allergists & Immunologists from India, American Society for Indian Anesthesiologists, Asian American Gastroenterology Physicians of Indian Origin (AAGPIO), American Association of Cardiologists of Indian Origin (AACIO), American Association of Obstetrician & Gynecologists of Indian Origin, Association of Indian Neurologists in America (AINA), Association of Asian Indians in Ophthalmology, Society of Orthopedic Surgeons in North America, American Association of Otolaryngologists of Indian Heritage, Indo-American Psychiatric Association (IAPA), American Association of Radiologists of Indian Origin, American Association of Physicians of Indian Origin -Sleep (AAPIOS), and Indian American Urological Association and others, will use JAAPI as a platform for their publication and outreach needs. These will be winning opportunities for all parties concerned. Networking and strengthening professional relations among specialty societies of Indian American doctors is the need of the hour. JAAPI offers an excellent platform for that. It is doable, especially in the post-COVID-19 pandemic period, which brought out the best in the medical, health care and scientific communities in the United States and rest of the world.

Journal of the American Association of Physicians of Indian Origin (AAPI)

Vision and Mission: JAAPI is a peer-reviewed medical and healthcare journal published by the AAPI. In line with the vision and mission of AAPI, JAAPI is dedicated to facilitate physicians to excel in patient care, teaching and research, and thus pursue their aspirations in professional and community affairs. JAAPI is open to contributions from physicians and scientists of all backgrounds and from all over the world.

Scope of JAAPI: JAAPI publishes a variety of articles, such as original research articles, clinical studies, reviews, perspectives, commentaries, case studies etc., covering all aspects of medical sciences, clinical specialties, and healthcare, including epidemiology, and policy, regulatory and legislative issues. Articles submitted to the JAAPI must be original and should not have been published or under consideration for publication elsewhere, except in abstract form in proceedings of conferences or meetings. Based on type of the article, the length and specifications vary. Only manuscripts that meet professional and scientific standards will be accepted for publication. Review process is single-fold blinded on the authors side. But after acceptance of papers, the names of the handling Editors and Reviewers will be published on the front page of the article. This new trend started by some European journals is gaining momentum as it gives due credit to the Editors and Reviewers and ensures fair review process.

Publication Model: JAAPI is published as completely Open Access in electronic form (PDF). These will be archived in AAPI website, and the link to URL for each issue will be emailed to AAPI Members. A few hard copies will be printed for promotional purposes and for displaying at AAPI Conventions and other professional meetings or for distributing to libraries or dignitaries. There will be no submission fee or publication charges to the authors. Although materials published are copyrighted by the AAPI, others can cite or reproduce figures, schemes and pictures published in JAAPI without paying fee, but by giving due credit to JAAPI. This does not apply for materials reproduced in JAAPI from other journals, which are copyrighted by the original publisher.

Registration and Indexing: After a year of publication or more, JAAPI will be eligible for applying for registration with MEDLINE. If successfully registered, JAAPI will be indexed in the PubMed operated by the National Library of Medicine. JAAPI will also be registered for indexing in other major bibliographic databases, such as SCOPUS (managed by Elsevier), EMBASE (Excerpta Medica Database), DOAJ (Directory of Open Access Journals), Ovid (Walter Kluwer Ovid Database) and BioMed Central Database. JAAPI will be added to ResearchGate, an European social networking site for scientists and researchers to share publications, discussions and collaborations. JAAPI will create a Twitter handle so physicians, healthcare professionals, academicians and scientists can follow the highlights of articles published in JAAPI.

Editorial Board: The Editorial Board of JAAPI consists of one Editor-in-Chief, several Deputy Editors covering different areas of medicine and health care, Editorial Board Members and Editorial Interns. In addition, there are Editorial Advisors to oversee performance and stability of JAAPI and to help the Editorial Board Members in logistics, administrative and fiscal issues. The Deputy Editors will handle the review process of submitted papers helped by internal (Editorial Board Members) and external reviewers. Editorial Interns are medical students or residents who would like to obtain training in editing for journals. They will work with the Deputy Editors. AAPI membership is required for all Editorial Board Members, who are expected to promote the vision and mission of AAPI through JAAPI.

CME Credits for Peer-Review Process: After indexing by PubMed, working through AAPI, JAAPI will obtain CME Credit eligibility for its reviewers by the Accreditation Council for Continuing Medical Education of the American Medical Association. Several journals are offering CME credits to their reviewers.

Journal Periodicity: Initially, JAAPI will have three issues per year (Spring, Summer, and Winter). As the journal picks up momentum and article submissions increase, the periodicity will be quarterly.

Types of Articles JAAPI Accepts:

- **Original Research Articles:** These describe original scientific or clinical research conducted on in vitro or animal models or human subjects after obtaining approval by the concerned institutional animal care and use committees or human subjects research review boards. The research should comply with the guidelines and regulations of US Public Health Service. The original research articles can be up to 3,500 words in length, excluding title page, abstract, legends and references. Maximum 7 figures or tables are allowed. Additional figures or tables need to be justifiable for the article. Supplemental Information (SI) containing data and text, such as methods, are allowed for deposition.
- **Review Articles:** The review articles can address any contemporary issue in medical or clinical sciences, or healthcare, including epidemiology, and policy, regulatory and legislative issues. The reviews should provide in depth analysis of the topics but should not be just presenting catalog of information. The review articles should be balanced and should cite literature without bias. The review articles can be 3,000 to 5.000 words, excluding title page, abstract, references, and legends. Not over 5 figures and tables combined. There is no limit on the number of references, but they should be recent and relevant ones.
- **Clinical Studies:** Clinical studies can be observational or retrospective analysis of data or prospective randomized studies. All clinical studies should be conducted under the regulations and guidelines, documenting informed consent, protection of research subjects, inclusion of minorities etc., as per the guidelines of the US Public Health Service. Rigorous statistical analysis should be followed. Raw data should be provided for analysis if required. These articles can be up to 5,000 words, excluding title page, abstract, tables, legends, and references. Maximum number of figures or tables are 7 combined. Additional figures or tables should be justifiable for the study. Supplemental Information (SI) is allowed for deposition.
- **Brief Reports:** Brief reports of contemporary issues of high significance are accepted to disseminate information. These reports are up to 1,500 words in length, excluding title page, abstract, legends and references. About 4 tables or figures combined are permitted. Maximum 15 references are allowed.
- **Letters to the Editor:** Letters to the editors on topics of high importance or on the articles published in JAAPI are welcome. These should be focused and carry significant take home message, rather than a simple presentation of one's own perspective on the topic. These can be up to 600 words in length with 6 references, 2 small tables or figures maximum. The authorship should be limited to 2 or 3. No abstracts are allowed.
- **Articles on Diagnosis and Treatment Review:** Article describing latest methods, approaches and technologies in diagnosis and treatment can be up to 2,000 words, excluding title page, abstract, references, and legends. Figures and tables should be limited to five combined.
- **Case Studies or Clinical Challenges:** Case presentation with about 300 to 400 words, followed by discussion of 500-600 words, 1-2 small figures, and less than 10 references, are welcome. The authorship should be limited to 3 unless it involves trainees. Proof of patient consent should be provided.
- **Perspectives on Contemporary or Controversial Topics:** These should be thought-provoking with intuitive analysis rather than presentation of facts. Some speculation and hypothesis is permitted provided they are supported by rational analytical base. These articles can be up to 1,200 words, excluding title page, abstract, legends and references. Less than 3 tables or figures combined are allowed. References should be limited to the required ones.
- **Commentaries on Published Papers:** Commentaries on published papers are accepted if they provide a different post-publication perspective not explicit or missed in the original publications. These can either positively or negatively affect the original publication. But the emphasis is how the original publication can affect clinical practice or evidence-based medicine. These can be up to 1,200 words in length with one or two figures or tables, and limited references. No abstract is allowed. Authorship should be limited to one or two.

- **Bench-to-Bedside or Bedside-to-Bench:** Authors can take laboratory findings to clinical settings or bring clinical dilemmas to laboratory research. Special emphasis should be made on moving the subject from bench to bedside or vice versa. This type of articles can be up to 1,200 words in length, excluding title page, abstract, legends and references. Not over 3 tables or figures combined are allowed. References should be limited to the required ones.

References Style: JAAPI follows the same style as JAMA for presentation of references, which can be found in the following URL. https://www.bibguru.com/c/jama-citation-generator/

Disclosures: All authors should disclose industry relations, including speaker's bureau, research grants, travel funds, stocks over $10,000 owned by them or their immediate family members, etc., which can be construed as conflicting with the content of the article being submitted. When in doubt whether a particular industry relation is a conflict, the authors should consult the editorial office.

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Proprietary Names: While citing names of drugs or medications, authors should avoid brand names and use generic or pharmacological names only.

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Contact Information: A dedicated portal for JAAPI will be created in AAPI website soon. Until that time, for further information about JAAPI or to submit articles, please email to jaapi@aapiusa.org.

Clinical Study

Impact of COVID-19 Pandemic on Outpatient Visits, Hospital Admissions, and Immunization Rates of Infants and Children in Pediatric Department of a Tertiary Care Center from Rural India

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Background: Healthcare facilities across the world are facing unprecedented challenges due to the COVID-19 pandemic. The imposed restrictions curtailing movement, transportation and fear of contracting infections from healthcare facilities has led to a likely delay in health seeking behavior among children. This study therefore aims to determine the impact of the COVID-19 pandemic on health services utilization by children for non-COVID illnesses and the rates of immunization in a tertiary care hospital in rural India.

Materials and Methods: This is a retrospective study from a tertiary care hospital in rural India. The monthly data for pediatric out-patient visits, total number of admissions to the pediatric ward, neonatal and pediatric intensive care units, total deliveries and the number of children visiting the immunization clinic for Pentavaccine I, II and III during the pandemic period from April 2020 to March 2021 and two pre-pandemic years from April 2019 - March 2020 and April 2018 - March 2019 were collected from the hospital information system. The mean (± standard deviation) of monthly utilization of services over a 12-month period during the pandemic were compared to the previous two pre-pandemic 12-month periods using one way ANOVA followed by post hoc Tukey HSD test. The significant p - value was set at <0.05.

Results - The number of children visiting the Out-patient unit during the pandemic period was decreased by 84% and this reduction is significant compared to the previous two pre-pandemic years ($p < 0.00001$). The admission rates of the pediatric ward had also significantly decreased during the pandemic months compared to a similar period during the previous two years ($p < 0.000018$). Similarly, the neonatal intensive care unit admissions and total deliveries had significantly reduced during the pandemic months compared to the previous two years for same period ($p = 0.007$ and $p = 0.00001$, respectively). The immunization rate for all the three doses of Pentavaccine had also significantly reduced during pandemic months ($p = 0.00001$) and only 47%, 38% and 34% infants visited the facility for Pentavaccine I, II and III, respectively.

Conclusion: We report a significant reduction in utilization of healthcare facilities by children for non-COVID-19 illnesses, and significantly reduced immunization rates among infants at the pediatric department of a tertiary care hospital in rural India.

Key Words: Admission Rates; Immunization Rates; Neonatal Admissions; Pediatric Intensive Care Unit; Total Deliveries.

Introduction: The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causing Coronavirus Disease (COVID-19) emerged from the Hubei province of China in late 2019 and was declared a pandemic by the World Health Organisation (WHO). India reported its first case of COVID-19 in January 2020. Over the next two months, there were 1400 infected cases and 47 deaths due to COVID-19. By April 2020 the number of cases in India increased by 23-fold. The rise in cases burdened the healthcare facilities and posed unprecedented challenges.

Hence, the Indian government took certain measures to control the spread of the virus. These included imposing social distancing, isolation of infected people, quarantine of their contacts, and a nationwide complete lockdown. The nationwide lockdown was enforced on March 34, 2020, and was eased in a phased manner until November30, 2020. These measures helped in reducing the transmission of infection and provided much needed time to healthcare facilities to prepare themselves to tackle the increasing demands.

With cases rising daily in number, many healthcare facilities were converted to dedicated COVID-19 centres. Routine outpatient and inpatient services were halted for non-COVID-19 illnesses. Many hospitals reassigned their staff to the care of COVID-19 patients, resulting in discontinuation of routine care of patients with chronic diseases and a disruption in routine immunization drives for children. Health professionals raised concerns regarding interruption to care of children with chronic diseases and cancers, and the interruption of routine vaccination drives could possibly result in emergence of vaccine preventable diseases. The travel restrictions, conversion of health facilities into dedicated COVID-19 facilities, discontinuation of routine vaccinations and fear of contracting infections from hospitals made it difficult for parents and children to seek help for medical emergencies and non-COVID-19 illnesses.

Objective: Since the focus of the government and healthcare providers shifted to serve the needs of COVID-19 patients, it was feared this would increase the long-term morbidity and mortality in children and neonates. Hence, we studied the impact of the COVID-19 pandemic on the utilization of healthcare facilities by infants and children for non-COVID-19 illnesses, and the routine immunization of pediatric patients at the pediatric department of a tertiary care hospital in central India. The hospital serves the rural population of Wardha and adjoining districts of Maharashtra and the neighbouring States.

Materials and Methods:

Study Design: This is a retrospective study from the Department of Pediatrics, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India.

Study Population: The following subjects were included in the study. Children below the age of 13 years visiting the out-patient unit, admitted to the ward, and pediatric intensive care units for non-COVID-19 related illnesses; infants visiting the immunization clinic for vaccination with Pentavaccine I, II and III; and total deliveries in the hospital, and newborn babies admitted into the neonatal intensive care unit.

Data Collection: The monthly data for outpatient visits, total number of admissions in the pediatric ward and neonatal and pediatric intensive care units, total deliveries and number of children visiting the immunization clinic for Pentavaccine I, II and III during the pandemic period of April 2020 to March 2021, and pre-pandemic periods of April 2019 - March 2020 and April 2018 - March 2019 were collected from the Hospital Information System (HIS). The mean (± standard deviation, SD) of monthly utilization of services over a 12-month period during the pandemic were compared to the previous two pre-pandemic 12-month periods.

Data Analysis: Data were presented as mean ± SD for each group. The statistical comparison for independent measures was done by processing raw data by one-way analysis of variance (ANOVA) followed by a post hoc test, namely Tukey HSD (Honestly Significant Difference) test. P values < 0.05 were considered significant.

Ethical Clearance: Ethical clearance for the study was obtained from the Institutional Ethical Committee.

Results: The data for the pre-pandemic and pandemic years are presented in the Table and the monthly trends are presented in the Figures 1 through 8.

Out-patient Department Visits: The number of children visiting the out-patient unit during the pandemic period ($n = 6587$) were significantly reduced compared to the pre-pandemic prior 2 years ($n = 39{,}723$ and $n = 35{,}712$) ($p < 0.00001$).

Inpatients Admissions: The admission rate was 40% during the pandemic period compared to a similar duration in the previous year. The admissions in pandemic period ($n = 1646$) was significantly reduced compared to the prior non-pandemic years ($n = 4051$ and $n = 4503$) ($p < 0.000018$). The seasonal increase in hospitalizations for viral illnesses was not observed during July through November months during pandemic months compared to previous years.

Table 1: Data for the Pandemic and Pre-pandemic Periods	Pre-pandemic Period 1 (April 2018-March 2019)[§]		Pre-pandemic Period 2 (April 2019-March 2020)[§]		Pandemic Period (April 2020-March 2021)[*]	
	Total (n)	Monthly Mean ± SD	Total (n)	Monthly Mean ± SD	Total (n)	Monthly Mean ± SD
Out-patient Visits	35712	2976 ± 826	39723	3310 ± 911	6587	549 ± 129
Admissions						
Pediatric Ward	4503	375.2 ±144.8	4051	337.5 ±128.7	1646	137 ±24.5
Pediatric Intensive Care Unit	447	37.2 ±35.9	508	42.3 ±26.1	242	20.1 ±10.4
Neonatal Intensive Care Unit	686	57.1±13.6	747	62.2 ±11.3	504	42 ±11.3
Total Number of Deliveries	5239	436.5±52.8	4995	416.2 ±42.2	3664	305.3 ±58.7
Immunization						
Pentavaccine I	912	76 ± 18.5	794	66 ±8.2	372	31±8.1
Pentavaccine II	716	59.6±14.7	657	54.7±8.6	251	20.9±5.8
Pentavaccine III	756	63±13.1	614	51.1±9.6	212	17.6±3.9

[*]All monthly values, except pediatric intensive care unit, differ significantly from the pre-pandemic periods 1 and 2

[§]There were no statistically significant differences between the two pre-pandemic periods

Pediatric Intensive Care Unit: The number of admissions in the pediatric intensive care unit was reduced by 53% during the pandemic period compared to a similar period in the previous year. However, this was not statistically significant (p = 0.11).

Neonatal Intensive Care Unit (NICU): The number of admissions in the neonatal intensive care unit was significantly reduced during the pandemic period (n = 504) compared to similar pre-pandemic periods (n =747 and n = 686) (p = 0.007). Neonatal intensive care unit admissions during pandemic period were 33% less than the pre-pandemic period of previous year.

Total Number of Deliveries: The total number of deliveries during the pandemic months was 27% less than that of the previous year. There was a significant reduction in the delivery rate during pandemic period (n = 3664) compared to previous pre-pandemic years (n = 4995, n = 5239) (p – 0.00001),

Immunization: The number of infants visiting the immunization clinic for Pentavaccine I, II and III was only 47%, 38% and 34%, respectively for the pandemic period of April 2020 - March 2021 compared to the period of April 2019 - March 2020. There was significant reduction in the immunization rate for Pentavaccine I, II, III during the pandemic period (n = 372, n = 252, n = 212 compared vs. n = 794, n = 657, n = 614 and n = 912, n = 716, n =756 during the non-pandemic periods (p = 0.00001)

Discussion: In this study, we report the impact of COVID-19 on the number of hospital visits, admissions in the pediatric ward, intensive care units, the number of deliveries and vaccination with Pentavaccine in the pediatric department of a tertiary care hospital in rural India. We observed 84% reduction in outpatient visits during the pandemic period of April 2020 - March 2021 This can be attributed to various travel restrictions imposed due to the lockdown and parental reluctance due to fear of their children contracting the disease. This delay

or avoidance in seeking medical help might have resulted in an increased number of children presenting late to the hospital with high morbidity. The pediatric ward and intensive care unit admissions were reduced by 60% and 53%, respectively during the pandemic months. This reduction in the admission rate in the ward and intensive care units is worrisome. A similar reduction in emergency room visits and out-patient visits was also reported by other investigators. (1-5)

Figure 1- Monthly Visits in the Outpatient Department

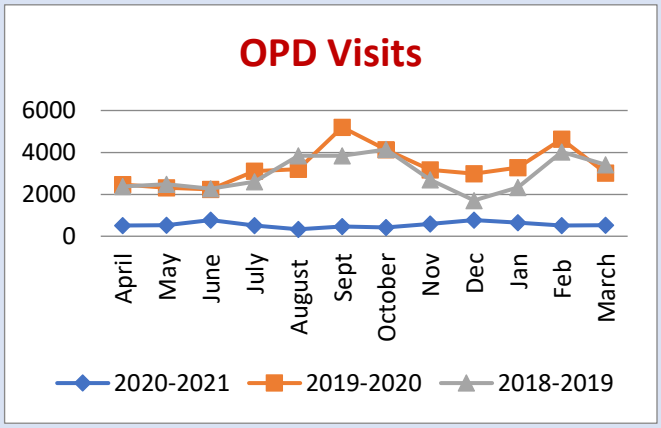


Figure 2- Monthly Admissions to Pediatric Ward

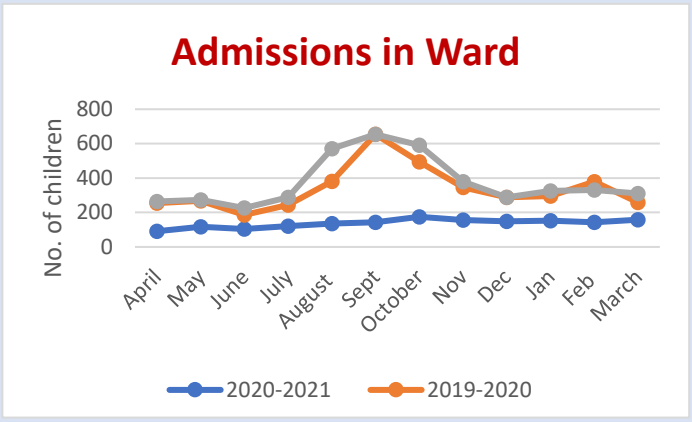


Figure 3- Monthly Admissions in Paediatric ICU

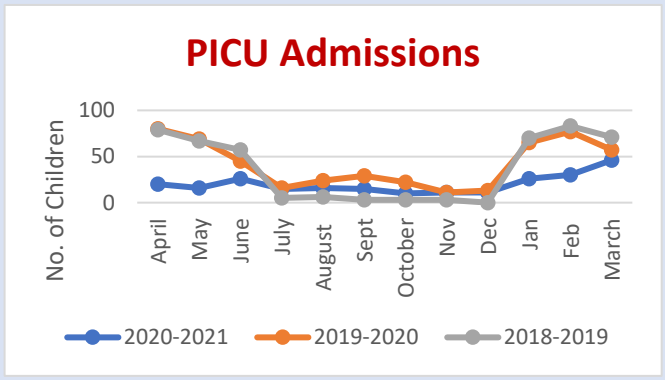


Figure 4 - Monthly Admission in Neonatal ICU

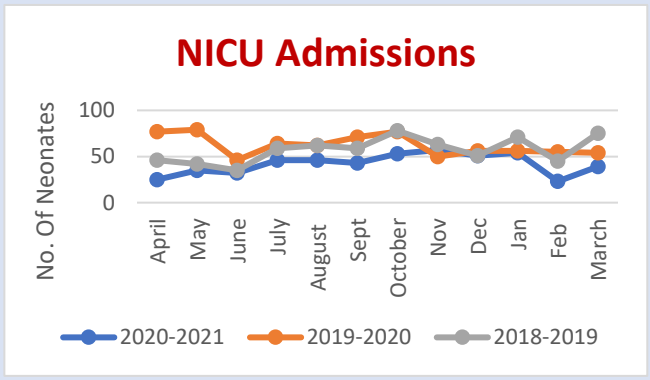


Figure 5 - Monthly Number of Deliveries

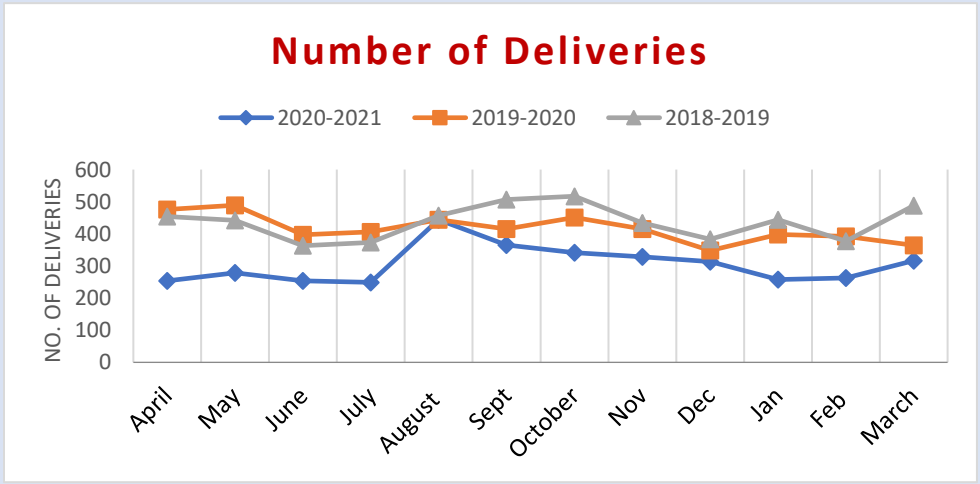


Figure 6- Monthly Data for Pentavaccine I

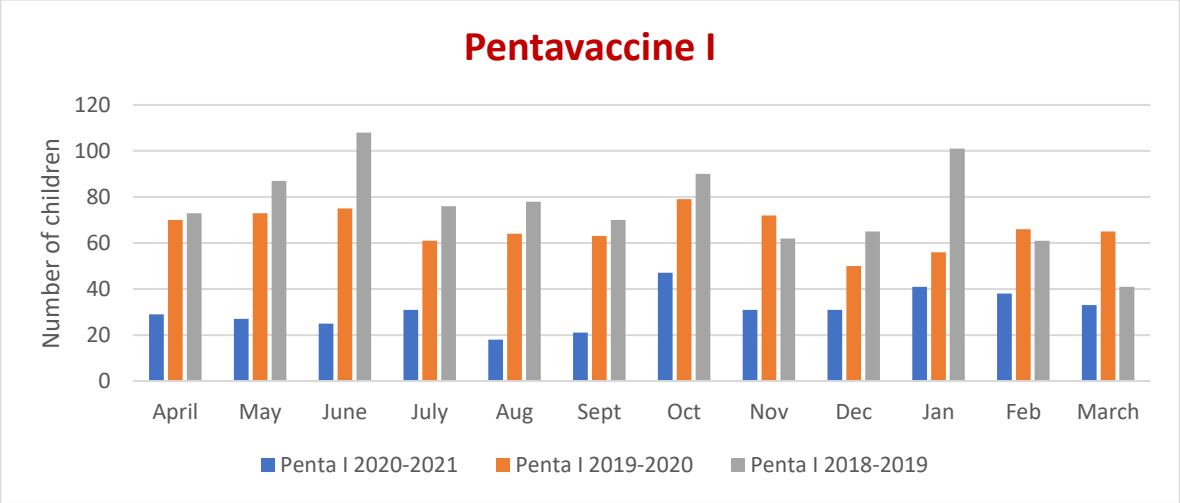


Figure 7- Monthly Data for Pentavaccine II

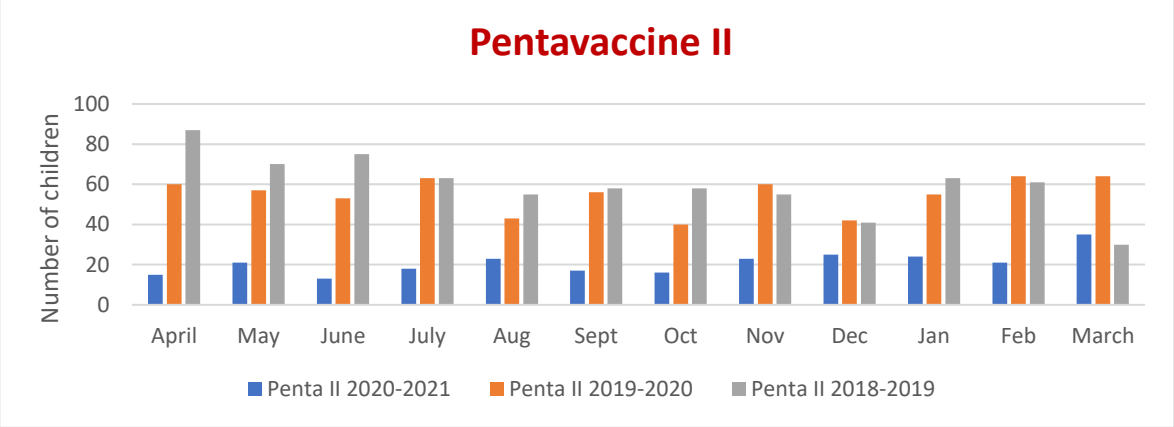
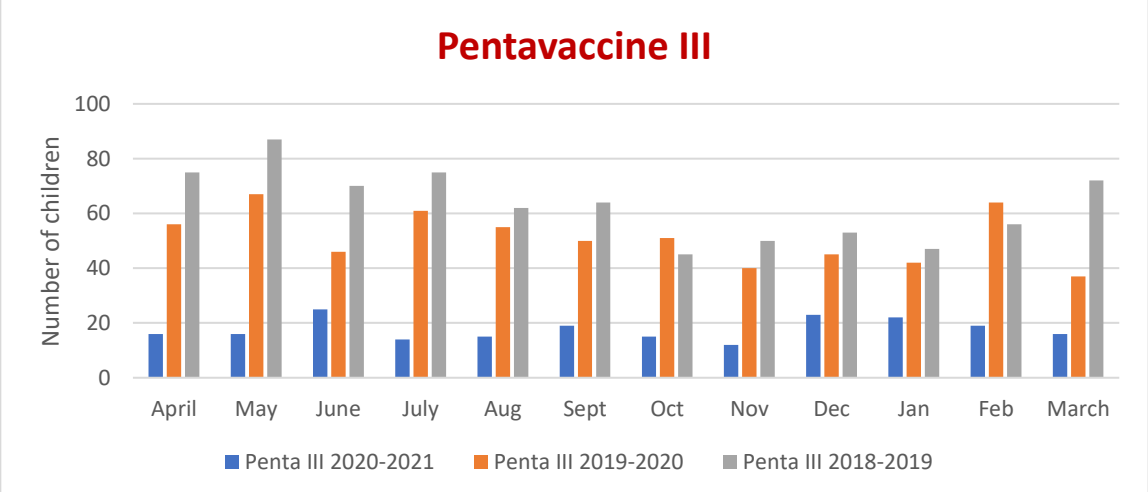


Figure 8- Monthly Data for Pentavaccine III



We observed a 27% reduction in total number of deliveries and a 33% reduction in neonatal intensive care unit admissions during the pandemic period from April 2020 - March 2021 compared to the preceding non-pandemic years. In a similar study from Ghana, Abdul-Mumin et al reported a significant reduction in neonatal intensive care unit admissions during the COVID=19 pandemic (6). The reduced number of deliveries imply these pregnant women delivered either at home or at healthcare centres with suboptimal facilities. This may have increased the risk of complications in mothers and newborn, especially in those with high risk pregnancies. The possibility of life-threatening conditions in neonates such as birth asphyxia, neonatal sepsis, and neonatal deaths, is also expected to increase due to reduced number of hospital deliveries. We observed a significant reduction in immunization rates for Pentavaccine I (47%), II (38%) and III (34%) at our immunization clinic which reinforced the concern regarding the negative impact of the ongoing COVID-19 pandemic on routine vaccination drives, as raised by an Experts Advisory Committee (7). Such reductions in immunization rates were also reported from Pakistan by Subhash Chandir et al. (8). The significant reductions may negatively affect herd immunity and the possibility of new epidemics due to vaccine preventable diseases (9-11).

The COVID-19 pandemic has disrupted routine healthcare globally. As healthcare facilities across the world are prioritizing care for COVID-19 patients, our results demonstrate that routine pediatric care is not immune to these COVID-19 related disruptions. Nationwide lockdown, home isolation, and fear of contracting infection from hospitals among parents prevented children with non-COVID-19 illnesses from seeking timely medical help. To minimise the adverse impact of the underutilization of routine and emergency health services, hospitals and health providers need to strategize and plan towards addressing the needs of children with illnesses other than COVID-19. Healthcare institutions should closely monitor their metrics such as outpatient department visits, inpatient admissions, and vaccination rates and ensure that they are aggressively brought back to pre-pandemic levels as and when the lockdown is gradually eased.

Conclusion: In this study, we report a significant reduction in utilization of healthcare facilities by children for non-COVID-19 related illnesses, and significantly reduced immunization rates in infants at a pediatric department of a tertiary care hospital in rural India. A comparison of data between the pandemic and pre-pandemic months suggests this reduction was not due to an annual changing pattern in the utilization of healthcare facilities.

Limitation of the Study: This is a rural hospital-based study. Hence the results cannot be extrapolated to the entire population of India. The study also does not consider parental views regarding the utilization of healthcare facilities during the pandemic and its after effects.

Conflict of Interest: The authors declare no competing interests.

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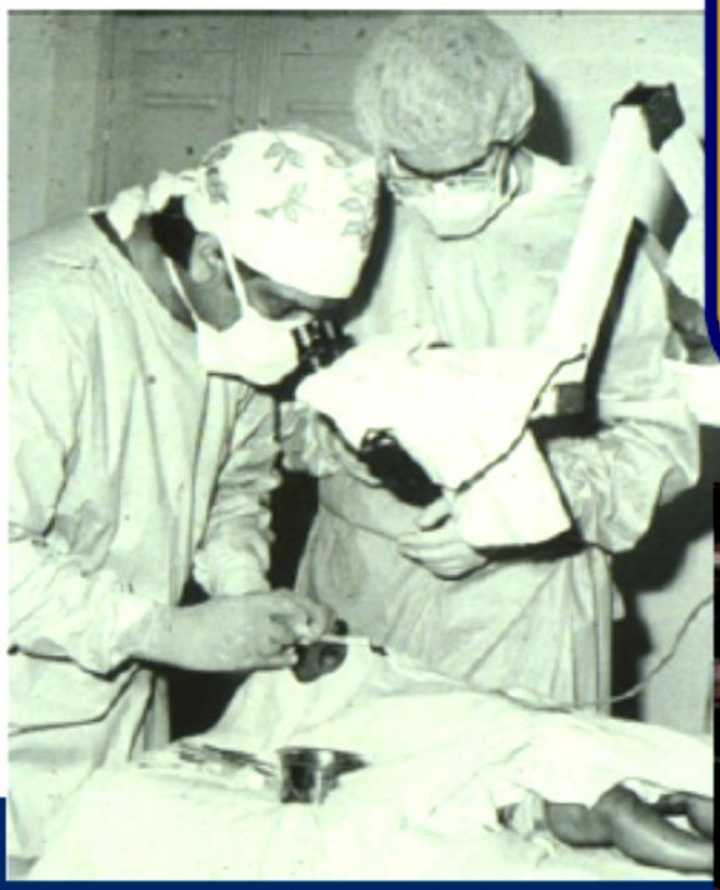

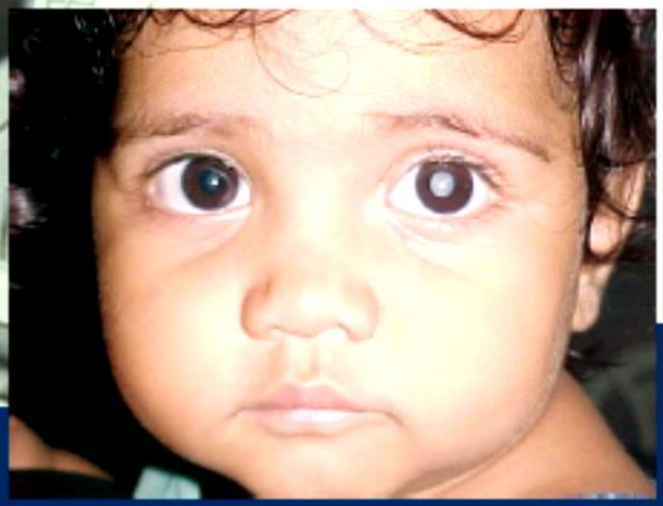

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In Depth Review Article

PROBIOTICS:
Genesis, Current Definition, and Proven Therapeutic Properties

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Abstract. This article focuses on probiotics, which impart several therapeutic benefits to improve human health. To eliminate the ambiguity, and skepticism on probiotics, the genesis of these miraculous micro-organisms which have evolved over millions of years, and how they became essential part of the human body are outlined. The role of World Health Organization (WHO) and Food and Agricultural Organization (FAO) for taking special interest to give universal definition on probiotics, and thus to encourage all countries to follow the same scientific path, has been outlined. This article also lists with explicit details probiotic strains belonging to several genera and species and their proven therapeutic benefits in preventing or curing major diseases or syndromes, with pertinent references. This review will immensely assist the medical practitioner to advice and recommend to their patient's specific blends of probiotics to prevent or treat their ailments with success, by considering the proven therapeutic properties of individual probiotic strains. In this respect, the article outlines several proven therapeutic benefits of naturally selected mixed strain undefined probiotic strains in homemade fermented buttermilk or Dahi or yogurt to improve the human health, illustrating how people in India thousands of years ago knew the health benefits of fermented products. The difference between the microbiota and microbiome has been explained with details, to eliminate the confusion of using these words, interchangeably. Specific details with bacterial numbers are also presented to show the importance of consuming probiotics on daily basis, and their role as an integral therapeutic components of human microbiota and microbiome.

Key Words: Multiple Mixed Strain Probiotics; Bacteriocins; Immunomodulins; Microbiome; Microbiota

Introduction: Probiotic is a Greek word where pro means "for" and bios means "life", This contrasts to antibiotic which derives from anti (against) and bios (life). Probiotics have been gaining popularity in the world due to their therapeutic uniqueness and their approved all-natural status, attested by several government organizations and their publications such as Food and Drug Administration (FDA) and Code of Federal Regulations (CFR) etc. (1,2,3). Several medical professionals are interested lately to know more about the genesis, physiological characteristics, health promoting properties, mechanism of reducing pathogenesis of certain disease, prophylaxis, prevention, and treatment applications about the probiotics. The World Health Organization (WHO) is heavily involved in this sector of science due to the ill effects or side effects attributed to the unscrupulous use of antibiotics, almost to the point of banning their use as therapeutic agents, in favor of probiotics. The world is after natural treatments which have no serious side effects. Using probiotics as nutritional supplements or probiotic therapy comes under the heading of "biologically based medical practices," according to the National Center for Complementary and Alternative Medicine (NCCAM), which is a Division of National Institutes of Health (NIH), which governs and defines the categories of the complementary and alternative medicine.

Sir Isaac Newton outlined in his Newtons third law of motion i.e., for every action there is an equal and opposite reaction. Antibiotics, which have saved so many lives, are now credited with the increase in the "superbugs", which have developed resistance to multiple

antibiotics. These superbugs are MRSA (Methicillin Resistant *Staphylococcus aureus*), C. diff (*Clostridium difficile*), species of Klebsiella, Carbopenium resistant Enterobacteriaceae etc. These pathogenic bacteria are typically hospital associated or acquired and they are named as nosocomial, or hospital acquired infections (4,5). Although hospital acquired infections are predominantly due to multiple antibiotic resistant pathogenic bacteria, one should not hesitate to include several viruses, including the causative virus of recent pandemic SARS-CoV-2 and their mutants, and several pathogenic yeasts (*Candida albicans*), and molds (causing mucormycosis).

The human fight against pathogenic microbes vs. pathogenic microbes fight against humans is an ongoing battle. However, our utmost understanding of the nature and physiology of a particular microbe gives us a competitive edge to destroy it. If not, microbes will take over and create misery to the humanity. This has happened during COVID-19 pandemic and 1918 Spanish flu, and the problems medical community is facing with nosocomial infections. One thing is for sure, and we have to accept the truth that nature gave an equal opportunity to every life to survive and to propagate their species, despite the adverse conditions and challenges they face. This is the reasoning behind the mutation of both bacteria and viruses. We have witnessed this in the past few decades by observing the emergence of multiple antibiotic resistant superbugs (bacteria) and continuous viral mutations of SARS-CoV-2 virus. The virus is attacking the population deficient in their immune system, perhaps due to underlying comorbid conditions or due to old age related immunoscenescence. Even with new vaccines, the constant viral mutation is making it difficult to immunize successfully the entire human population, with no relapse. Regarding nosocomial infections, the only treatment modality left is biological therapy using Multiple Mixed Strain Probiotics (4,5,6).

The nature has also given us probiotics as an all-natural biological therapeutic agents to counteract the pathogenic bacteria and viruses, despite their mutations along with our own active innate and adaptive immune systems. A philosophical question to be asked is why are several pathogenic bacteria and viruses are raging more wars against human race more recently, in the past few decades, than before? The answer to this puzzle is it is human negligence and lack of understanding of the nature and the natural eco-system. Humans assumed it ignorantly that they may destroy the nature, which ultimately resulted in the disturbance of eco-balance. To put it in simple words, we have grossly misused several antibiotics and drugs which altered the composition of human microbiota and microbiome and thus the immune system. These are conducive to encourage mutations in both the pathogenic bacteria and in viruses, as a protective measure to safeguard their species. Ultimately, these abnormal mutations have created superbugs and pandemic creating viruses. One of the best ways to get around this problem is through understanding, proper usage, and optimal maintenance of probiotics in GI tract microbiota, which will confer immunity to override these mutated pathogenic bacteria and virus through immune-modulation.

What are Probiotics? Although the scientific community knew benefits of the micro-organisms in the gastro-intestinal tract for some time, the term probiotic was only coined in the year 1965 by Lilly and Stillwell in a context other than probiotics influence on promotion of health (7). Parker in the year 1974 described probiotics as organisms and substances which contribute to intestinal microbial balance (8). Fuller in 1989 has redefined probiotics as live microbial supplements which beneficially affect the host by improving microbial balance (9). Salminen et al, in 1998 defined probiotics as foods containing live bacteria beneficial to health (10). In the year 2001, United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) with the Canadian Research and Development Center for Probiotics, came up with the following consensus definition for probiotics, which is: *Probiotics are any live micro-organisms which when administered in adequate amounts confer a health benefit on host.* This is the accepted and widely used definition which encompasses all application of live micro-organisms, not just those for the gastrointestinal health benefits (11,12).

The term micro-organisms defines any organism which can only be seen under microscope. Generally, probiotics include bacteria, few yeasts such as *Saccharomyces boulardii*, and food grade safe molds such as *Penicillium roqueforti* and *Penicillium camembertii*. It is worthwhile to mention the relative sizes of the probiotic bacteria, yeasts, and bacterial virus. The size of single bacterial cell is 1 to 2 microns, where micron is one millionth of a meter. The single yeast cell may be approx.-imately 5 to 10 microns in size which can be viewed under a light microscope. The viruses which attack probiotic bacteria are called bacteriophages and their size is 30 to

100 nanometers, where nanometer is one billionth of a meter. The SARS-CoV-2 virus, which create COVID-19 pandemic, is approximately 70-100 nanometers in size and thus can only be seen under an electron microscope (13).

The entire bacterial population in the human gastrointestinal tract is approximately 100 trillion, whereas the total human cells in the entire body are approximately 10 trillion. The human has ten times more bacterial cell population than the total human cells. One hundred trillion bacteria in the human gastrointestinal (GI) tract are represented by approximately 1000 microbial genera and species, with diverse physiological functions. The total represented by various genera and species is called microbiota. Whereas the total of genes in the microbiota (total microbial population in human) is termed microbiome (14). Each human cell has approximately 20,000 genes, whereas smallest bacterial cell has about 500 to 1000 genes, and the larger size single bacterial cell may have approximately 5000 genes. If we pool the total genes present in all cells in a human body, we will have approximately 200,000 trillion genes. This contrasts with the number of genes present in the bacterial population present in the human gastrointestinal tract, which is 250,000 trillion. In simple terms, the bacterial genome is equal to or more than human genome, and the significance of which is not understood, in terms of maintenance of human health.

About 20% of the total GI bacteria may be probiotics, which are considered therapeutic segments of microbiota, that can confer health to humans. The rest 80% of microbiota may have diverse functions such as improving digestion, producing vitamins, and protecting the epithelial cell integrity etc. Thus, mathematically around 20 trillion bacteria out of 100 trillion are probiotics (15). The generally asked question by physicians, is there any set number of probiotic bacterial cells to be consumed by patient to derive the maximum health benefit? A commercially available capsule of probiotics, weighing approximately 500 mg, has one billion organisms at the time of inception. At the time of consumption, the viable (colony forming units) probiotics may only be a maximum of 50 million. When such a capsule is administered orally, perhaps only one half of the probiotic population may survive in the stomach (due to low pH). So, only a maximum of 25 million organisms reach the ileum alive, after they are exposed to bile juice. Out of these 25 million organisms, a maximum of 2.5 million gets to stick to the receptor sites, after competing with over 100 trillion bacteria present in the GI tract.

Thus, 2.5 million new probiotic bacteria in 100 trillion gastrointestinal tract are negligible and minuscule. Hence, a daily ingestion of viable probiotics along with their growth end products (immunomodulins) is the process to derive the maximum benefit (15). Once again, physicians have to consider the individual genera and species of probiotic bacteria present in the commercially available mixed strain probiotic preparations to properly advise their patients. The total probiotic bacterial number (in a capsule or tablet) alone should not be the criteria to select the probiotics, if such probiotics do not have immunomodulins or the growth end products in the preparation.

The probiotic bacterial growth end products are termed-immunomodulins. Unfortunately, most of the commercial probiotic preparations do not have immune-modulins, since the manufacturer is only concerned about total bacterial numbers to sell their products. Even if the number of bacteria is less, such probiotic preparations in the presence of immunomodulins will exhibit better therapeutic effect (15).

Genesis of Probiotic Bacteria: A commonly asked question is how old are these probiotic bacteria and when did they come into existence into this world? If life started on this planet around 3.5 billion years ago, perhaps bacteria in general (not specially probiotics) can be only 1.8 billion years old. Scientifically, bacteria were observed for the first time by Antonie van Leeuwenhoek in 1676 with the newly invented primitive microscope. In the late 1800's Louis Pasteur and other scientists came up with the concept stating that some pathogenic bacteria are responsible for certain types of diseases, which was termed the "germ theory." Dr. Metchnikoff, a Nobel Laureate, in 1908 came up with a hypothesis that certain bacteria, specifically belonging to genus lactobacillus, present in the human GI tract can prevent intestinal putrefaction and thus can improve overall human health and longevity (16). Thus, Metchnikoff had been credited as Father of Probiotics, although the word probiotic was not coined until the year 1965 (17).

Although microbiology is of recent origin, cultured buttermilk (undefined bacterial fermentation of milk) was prepared and consumed daily in Indian households to improve their health for over hundreds or thousands of years. For thousands of years Indians have practiced the

art of fermenting milk using a biological agents present in the nature, which are beneficial bacteria, more specifically probiotics (17). The inoculum they were using probably had several undefined beneficial lactic acid producing bacterial species. To date, the practice of making cultured buttermilk, using previous days inoculum, is being practiced daily in each Indian household. Perhaps, the inoculum may be few thousand years old, and households guarded it with utmost care. Such fermented buttermilk will have at least 100 million beneficial nature provided probiotic bacteria per gram or milliliter, and each person consumes at least 250 ml per day as part of the meal. In mathematical terms, each individual in India potentially consumes minimum of 25 billion live (colony forming units) probiotic bacteria, along with their growth end products (immunomodulins) per day throughout the life.

This old practice of consuming probiotics daily started apparently around 5000 years ago as evident from the Indian scriptures. This discovery must have been made serendipitously. Homemade buttermilk in India has naturally selected lactic acid bacteria, which have been acclimatized over years with no strain domination. Technically, according to the definition of WHO/FAO, homemade Indian cultured buttermilk or Dahi or curd qualifies as probiotic. I would venture to say these undefined bacterial cultures (probiotics) in homemade cultured buttermilk or Dahi in India are naturally phage resistant and, also produce significant amount of immunomodulins including several bacteriocins and therapeutic peptides.

It is also believed that some of the lactic acid bacteria (probiotics), over the time (perhaps over million years) built genes (plasmids) to code for to produce specific enzymes such as lactase (β-galactosidase) and casein (milk protein) breaking enzymes, to digest the complex sugars (disaccharide-lactose) and complex proteins (caseins) of milk origin. These plasmids are circular and divide autonomously during cell division and thus pass onto the daughter cells, assuring that their therapeutic functions are maintained from generation to generation. With these naturally synthesized plasmids and other chromosomal genes these probiotic bacteria produce specific therapeutic end products of their digestion called immunomodulins. Thus, lactic acid bacteria (probiotics) have intrinsic capacity to not only compete with pathogenic bacteria due to their innate ability but also exert immunomodulation through immunomodulins (18).

Scientifically and Clinically Proven Therapeutic Properties of Probiotic Bacteria: The following are some of the beneficial properties of probiotic bacteria to improve the human health

Table 1: Therapeutic Properties of Probiotics

Therapeutic Properties
Reduction of lactose intolerance (18)
Reduction of viral infections – traveler's diarrhea and roto virus diarrhea (18, 19)
Reduction of Intestinal bacterial infections (19)
Reduction of hypertension and heart disease (19)
Reduction of serum cholesterol and triglycerides (20-23)
Reduction of cancers (24)
Reduction of obesity, constipation, irritable bowel syndrome, autoimmune diseases, autism, and Parkinson disease (25, 26)
Reduction in allergies (26)
Reduction of Helicobacter pylori infections (25)
Improvement of immunity through immunomodulation (26)
Reduction of coronaviral infections (e.g., SARS-CoV-2)
Reduction of osteopenia and osteoporosis
Improvement of longevity (anti-aging)
Prevention and treatment of hospital acquired (nosocomial) infections

List of Probiotics and their Specific Therapeutic Functions: The latest definition of probiotics by WHO/FAO panel along with the Canadian Research and Development Center is: *Probiotics are any live micro-organisms when administered in adequate amounts confer a health benefit on Host*. According to this definition, any

live micro-organism which is non-pyrogenic, non-pathogenic, and has GRAS status (Generally Regarded as Safe) according to FDA, produced under safe and suitable conditions under the inspection of FDA or local health departments, with a proven health benefit should qualify as probiotic. Several food grade micro-organisms can be categorized under this definition, besides the commercially known species belonging to genus Lactobacillus and Bifidobacterium. With research conducted on Para probiotics (inactivated probiotics along with their immunomodulins) and their influence on improving the immunity, even the organisms sensitive to acidic conditions in the stomach and sensitive to bile in the upper GI tract, can be coupled with the acid resistant and bile resistant strains of probiotics to arrive at multiple mixed strain probiotics, to maximize immunomodulation and the GI health.

In addition, some of these probiotics produce bacteriocins, which are highly effective to inhibit wide range of pathogenic bacteria. The bacteriocins differ from antibiotics. Unlike antibiotics (produced by molds or synthesized), the bacteriocins (produced by probiotics) are nontoxic and nonallergenic and can be ultimately inactivated by the specific enzymes in the human gastrointestinal tract, after they exert their specific function. The pathogenic bacteria cannot develop resistance towards bacteriocins, unlike antibiotics. The bacteriocins produced and excreted by probiotics are ribosomal synthesized antimicrobial peptides. The bacteriocins produced by probiotics are divided into four classes (Class I to IV) based on their amino acid composition, heat sensitivity and inhibitory patterns on pathogenic bacteria, according to Klaenhammer (27), and Nes et al (28). The probiotic produced bacteriocins also have significant immunomodulation besides inhibiting several pathogenic bacteria. Class I bacteriocins are small and heat stable and have post translationally modified amino acids and are also termed lantobiotics. These are produced by lactic acid producing probiotic bacteria belonging to genus Lactococcus and are highly effective and have broad inhibitory spectrum against Gram positive pathogenic bacteria, clostridium, and bacillus spores. Class II bacteriocins are considered non-lantobiotics, and are also small like Class I, with 30 to 100 amino acids, and are heat stable and very effective in inhibiting pathogens like listeria etc. Class III bacteriocins produced by species of the genus Enterococcus and *Lactobacillus helveticus* are large in size, 730 kilo Daltons, and are heat labile. They also exhibit inhibitory properties against several pathogenic bacteria. The Class IV bacteriocins are complex with glycol and/or lipid moieties.

The other immunomodulins produced (besides bacteriocins) by probiotics are, molecular hydrogen peroxide, organic acids such as acetic, lactic, butyric, and propionic acids, and also several specific and nonspecific bio-therapeutic peptides and short chain fatty acids etc. These immunomodulins have several functions because they exhibit antibacterial effect on pathogens, strengthen the intestinal epithelial cell barrier, stimulate the growth of other beneficial bacteria of the GI tract, maintain optimum ratio of various species in the microbiota, and finally activate the lymphatic system to exert proper immunomodulation.

Although, it is beyond the scope of this article, it is worthwhile to make a brief mention of prebiotics, which stimulate probiotics, to improve their therapeutic efficiency. Prebiotics are not micro-organisms, and these are the food ingredients specifically to stimulate probiotics through synbiosis. Most of these prebiotics cannot be digested or absorbed in the human GI tract, since humans lack specific integral enzymes. Yet they can be digested and assimilated by probiotic bacteria, to build up their population to enhance both the microbiota and microbiome, and thus to improve the health of the host. The classical examples of prebiotics are inulin, an oligosaccharide etc., which are dietary fibers. The fructo-oligosaccharide is effective as a prebiotic. In addition, several herbs serve as prebiotics. The probiotic bacteria digest prebiotics to produce short chain fatty acids, which not only serve as nutrients to the host but also helps to maintain the balance of microbial species involved in GI tract microbiota through positively associated growth relationships.

The following are probiotics (identified with their genus an species) proven to have prophylactic or clinical therapeutic effects (29-32), to improve human health: *Lactobacillus plantarum* (33), *Lactobacillus rhamnosus* (33); *Lactobacillus paracasei* (33); *Lactobacillus casei* (*34*); *Lactobacillus helveticus* (35-39); *Bifidobacterium bifidum* (40); *Bifidobacterium longum* (40); *Streptococcus thermophilus* (40-42); *Lactobacillus bulgaricus* (43); *Lactobacillus sporogenes* - also called *Bacillus coagulans* (44); *Lactococcus lactis* subsp. lactis (45); *Lactococcus lactis* subsp. cremoris (46); *Lactococcus lactis* subsp. lactis var diacetylactis (46); *Streptococcus faecium* (46); *Lactobacillus acidophilus* (*47 and 48*); *Pediococcus acidolactici*

(49); *Propionibacterium shermanii*, *Propioni-bacterium arabinosum*, and *Propionibacterium jensenii* (50-55); *Brevibacterium linens* (56); *Penicillium roquefortii* and *Penicillium camembertii* (57); and *Sacchromyces boulardi* (57). Without an exception all these probiotics significantly improve immunity through immunomodulation and thus also contribute to antiaging (58).

Tables 2 and 3 outline the use of specific sets of (either single or multiple strains) clinically proven probiotics to prevent or assist to cure a specific disease or syndrome. These will serve as an excellent reference material to the physicians.

Table 2. Specific Probiotic Strains with Major Therapeutic Effects to Assist Reduction of Obesity – Blood Sugar, Cholesterol, Hypertension, Allergies, Viral Infections, Arthritis, and Cancer.

Obesity and Blood Sugar	High Cholesterol	Hypertension	Allergies	Viral infections	Arthritis	Cancer
**L. plantarum*	*Sacchromyces boulardi* *Penicillium roquefortii* *Penicillium camembertii* *Brevibacterium linens* *Lactococcus lactis subsp. lactis* *L. bulgaricus*	*L. plantarum* *Lactococcus lactis subsp. lactis* *L. helveticus*	*Lactococcus lactis subsp. cremoris* *L. plantarum* *L. acidophilus* *Streptococcus thermophilus*	*L. plantarum* *L. rhamnosus* *L. casei* *L. bulgaricus* *L. sporogenes* *Lactococcus lactis subsp. lactis*	*L. acidophilus* *L. helveticus* *L. casei*	*L. plantarum* *Lactococcus lactis subsp. lactis* *Propionibaterium shermanii* *Propionibacterium arabinosum* *Penicillium roquefortii* *Sacchromyces boulardi* *Brevibacterium linens*

Conclusion: The genesis and therapeutic benefits of several strains of probiotics belonging to different genera and species are outlined with explicit details and references. These should serve as a guide for physicians to recommend combination of probiotics as therapeutic aids to prevent or cure certain types of diseases. The difference between the microbiota and microbiome has been explained. The importance of probiotics, their percentage in total GI tract flora and their role as integral therapeutic components of human microbiota has been presented. The genesis of homemade Indian buttermilk with natural multiple mixed strain probiotics has been presented, to demonstrate the prevalence of probiotics use for over centuries, and how the ancient human civilizations took advantage of them to improve their immunity and health.

Disclosure: Author is a scientist heavily involved in probiotic research and holds over 150 US and International patents. His company (IMAC, Inc.) manufactures and sells food grade microbial cultures and other high tech essential enzymes fortified functional products that go into manufacturing cheese and other dairy products in the United States, Canada, Europe, Asia and South America.

Table 3. Specific probiotic strains with major therapeutic effects to assist reduction of lactose intolerance,-irritable bowel syndrome (IBS),-irritable bowel disease (IBD), sleep apnea, anxiety-depression, antibiotic associated diarrhea, fungal infections, immunosenecence in old age, and activation of immune system to override sluggish response to vaccination.

Lactose intolerance IBS, IBD	Sleep apnea	Anxiety-depression	Antibiotic associated diarrhea	Fungal infections	Immune-senecence	Sluggish response of vaccination
**L. plantarum* *L. paraceasei* *Bifidodacterium bifidum* *Bifidobacterium longum* *L. acidophilus* *L. sporogenes* *Streptococcus faecium* *Sacchrumyces boulardi* *Streptococcus thermophilus*	*L. helveticus* *L. acidophilus*	*Lactococcus lactis subsp. cremoris* *L. acidophilus* *L. plantarum* *L. helveticus*	*L. acidophilus* *Streptococcus thermophilus* *L. plantarum* *L. rhamnosus*	*Propioni-bacterium shermanii* *Propioni-bacterium arabinosum* *Lactococcus lactis subsp. lactis var diacetylactis* *L. acidophilus*	*L. casei* *L. helveticus* *L. acidophilus* *L. bulgaricus* *Sacchrumyces boulardi* *Lactococcus lactis subsp. lactis*	*Lactobacillus rhamnosus* *Lactobacillus sporogenes*

*L. stands for genera Lactobacillus

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AHA Guidelines Update

AHA 2020 Adult Resuscitation Guidelines and Interim Guidance during COVID-19 Pandemic: A Brief Review of 2020-2021 Updates

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Introduction: Sudden Cardiac Arrest (SCA) remains a leading cause of morbidity and mortality in the USA and worldwide. More than 347,000 adults and 7,000 children (<18 Y/o) suffer Out-of-Hospital Cardiac Arrest each year in the USA. In-hospital Cardiac Arrest affects approximately 292,000 individuals annually.

American Heart Association (AHA) previously published guidelines every five years until 2015, when a more continuous review process of research with updates was initiated. These guidelines are developed following structured evidence evaluation, analysis, literature cataloging, and scientific evidence reviews based on clinical efficacy, ease of implementation, and local systems factors.

Highlights of AHA 2020 Guidelines:

1.Reaffirmation of core resuscitation concepts: Early high-quality Cardiopulmonary Resuscitation (CPR) and Defibrillation
2. Recommendations on ways to increase CPR by lay rescuers, including the use of mobile technology
3. Updates addressing disparities in CPR training
4. Early administration of Epinephrine for non-shockable rhythm and early Defibrillation for shockable rhythm
5. New recommendations for treating Opioid Overdose, and Cardiac Arrest in Pregnancy
6. Increased ventilation rate for pediatrics
7. Focus on specialized resuscitation situations
8. Optimizing post-resuscitative care
9. Neuro-prognostication and addition of Recovery as part of the Chain of Survival

Recovery: Recovery /survivorship plans help guide the patient, caregivers, primary care providers, and include a summary of the inpatient course, recommended follow-up appointments, and post-discharge recovery expectations.

Neuroprognostication: Accurate neurological prognostication is essential to avoid inappropriate withdrawal of life-sustaining treatment in patients who may otherwise achieve meaningful neurological recovery. A multi-modal approach utilizes important tools: Imaging (Head CT), Electrophysiology, Clinical Examination, and Serum Biomarkers such as Neuron-specific Enolase.

Improving CPR Skill Acquisition and Retention: These include periodic booster training and feedback devices. Enhancing resuscitation training involves Teamwork and Leadership Training, In Situ Training, High-fidelity Manikins, Gamified Learning & Virtual Reality. The use of mobile phone technology by emergency dispatch systems to alert willing bystanders to nearby events that may require CPR or Automated External Defibrillator (AED) use is reasonable.

Cardiac Arrest due to Suspected Opioid Overdose: The mainstay of care involves initiation of the emergency response system and performance of high-quality CPR. For respiratory distress/failure: Prevention of deterioration and providing naloxone are priorities. Naloxone only reverses respiratory arrest due to opioid overdose. There is no evidence for its use in Cardiac Arrest due to non-respiratory causes.

Maternal Cardiac Arrest: The highlights focus on team-planning for "Maternal Cardiac Arrest" including using lateral uterine displacement and "Perimortem Delivery".

Targeted Temperature Management (TTM): TTM is a Class 1 AHA Guideline in resuscitated comatose patients. There are not enough evidence-based studies yet to support the advantage of 36° C compared to 32-33° C for cooling temperatures, and other issues.

Double Sequential Defibrillation (DSD): A recent sizable systematic review recommended against routine use of DSD. Unanswered questions remain about DSD, such as intershock timing, pad positioning technique, and the possibility of harm with increased energy.

AHA Interim Guidance of Resuscitation during COVID-19 Pandemic (2020 & 2021 Updates): About 12-19% of COVID-19-positive patients may require hospitalization, and 3-6% may be critically ill. Hypoxemic Respiratory Failure, Acute Respiratory Distress Syndrome, Myocardial Injury, Malignant Arrhythmias, and Shock lead to Cardiac Arrest. Drug-induced Arrhythmias with Hydroxychloroquine and Azithromycin (prolonged QT) also contribute to cardiac problems.

Exposure of Healthcare Workers: CPR involves aerosol-generating procedures (Chest Compressions, Positive Pressure Ventilation, and other Airway Interventions). Working in a closed environment with others, high-stress events leading to inadequate infection-controlled practices and lack of adequate Personal Protective Equipment (PPE) are serious concerns.

Reducing Provider Exposure:

Guidelines

1. Don PPE before entering the scene of resuscitation.
2. Limit Providers.
3. Replace manual chest compressions with mechanical CPR devices if available.
4. Communicate COVID-19 status beforehand.

Oxygenation and Ventilation Strategies with Lower Aerosolization Risk:

1. Attach a high-efficiency particulate air (HEPA) filter to any manual or mechanical ventilation path of exhaled gas.
2. First-pass intubation by an experienced provider with a cuffed tube early is recommended (Video-laryngoscopy if available).
3. Use a bag-mask device or T piece in neonates with a HEPA filter and tight seal. In adults, consider passive Oxygenation with a non-rebreathing face mask covered by a surgical mask.
4. Use a supraglottic airway or bag-mask device with a HEPA filter.
5. Briefly pause chest compressions to intubate.
6. Minimize closed-circuit disconnections.

Emergency Medical Services and Bystander Help: The prevalence of COVID-19 among Out-of-Hospital Cardiac Arrest patients is low (about 5%) in most communities compared to residential settings. However, risks and benefits need to be balanced in light of ongoing available evidence.

Alerting EMS (# 911) after prompt recognition of Sudden Cardiac Arrest should be followed by initiating high-quality Chest Compressions, and "Rescue Ventilation" in Children.

Immediate Defibrillation needs to be done when AED is available. Risk of transmission of severe acute respiratory syndrome seems to be low with Hands-Only-CPR and Public Access Defibrillation. Chest compressions and defibrillation are priorities for lay rescuers even when facemasks are not immediately available.

Transmission risk during aerosol-generating procedures can be reduced with Personal Protective Equipment.

Standards of COVID-19 care need to promote strategies keeping in mind the inequalities of geographic disease prevalence and resources for optimal outcomes.

In-Hospital Pre-arrest: Address Advanced Care Directives & Goals with COVID-19 patients/families ahead. Consider a negative-pressure room or unit.

In Intubated Patients:

A. Leave the patient on a mechanical ventilator with a HEPA filter.
B. Ventilator settings to allow asynchronous ventilation.
C. Increase Fio2 to 1.0 initially.

Settings: Tidal volume 4-6 ml/kg ideal body weight and 6 ml/kg for Adults with pressure or volume ventilation, Rate: 10 breaths/min for Adults and 30 breaths/min for neonates. Adjust PEEP as needed.

Prone Patients: For patients with suspected or confirmed COVID-19 in prone position with no advanced airway, it is recommended to place them in supine position for continued resuscitation. It is reasonable to leave intubated patients in prone position, if unable to safely change into

supine position. Place defibrillator pads in an anterior-posterior position and provide Prone-CPR with hands over T7/T10 vertebral bodies.

Maternal Cardiac Arrest: These are high-risk patients with poor outcomes. Initiate preparation early for "Perimortem Delivery" after 4 minutes of unsuccessful resuscitation (Obstetrical and Neonatal team readiness).

Rationale to Start and Continue Resuscitation: Mortality due to Cardiac Arrest in COVID-19 patients is very high (exact statistics not available). Consider age, severity, and co-morbidities in deciding, while balancing the risks to rescuers. Consider resources and future strategies.

Extracorporeal CPR: There are insufficient data to support Extracorporeal CPR for COVID-19 cardiac resuscitation.

Conclusion: The "2020 AHA Guidelines for CPR and Emergency Cardiovascular Care" and "Interim COVID-19 Guidance 2020 &21" provide a comprehensive review of evidence-based recommendations for resuscitation and emergency cardiovascular care. It is crucial to develop Institutional and resource-specific policies.

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Broad Review Article

Off-Label Use of Drugs:
Science, Clinical Usage, Ethics, Regulations and Liability

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Abstract: The term "off-label" is used when a drug is prescribed for conditions other than those for which it has been approved by the US Food and Drug Administration (FDA) or its equivalent in other countries. FDA regulates only approval of drugs for clinical use, but not how they are prescribed by physicians. So, legally physicians have the freedom to prescribe a drug for any reason or condition they consider medically appropriate, provided the drug is efficacious and safe to use in that particular disease. The economic benefits of off-label drug use (OLDU) are obvious. OLDU is very common in real world clinical practice. However, a vast proportion of these off-label prescriptions do not have scientific basis, suggesting that physicians rely more on their experience with the drugs and/or on their gut feelings and less on scientific evidence. Using off-label prescriptions without scientific evidence is associated with a significantly higher number of adverse events than the use with scientific evidence. Because of these safety concerns and potential ethical and liability issues, physicians need to exercise caution regarding OLDU. This broad review presents clinical use of off-label prescriptions in certain specialties; scientific, ethical, and medicolegal aspects of OLDU; regulations related to OLDU; economic impact of OLDU; potential negative consequences of OLDU on evidence-based medicine; the role of electronic prescription in promoting OLDU; and unsolved problems. This review empowers physicians by guiding how to protect their practice and to check for FDA-approved uses and scientific basis for OLDU. Finally, the review discusses the widespread and desperate attempts for OLDU in COVID-19 disease.

Key Words: Off-label use; FDA; Drug prescription; Drug safety; Drug efficacy; Medicolegal

What is OLDU? Off-label is defined as using pharmaceutical drugs for an unapproved use. The unapproved use can be related to the indication, age group, dose of the drug, route of administration, or formulation. An approved indication is when a government drug regulatory agency, such as the FDA formally agrees that the drug is medically appropriate for the named condition. Thus, the term "off-label" represents a regulatory term given by the FDA, and it does not have a negative connotation or implication (1). An approved indication may define the use based on medical condition, dose, patient's age, size and gender, conditions such as pregnancy or lactation or other medical conditions (2, 3). FDA regulates drug approval, but not drug prescribing. So, physicians can lawfully prescribe a drug for a condition they think medically appropriate, provided it is safe and efficacious to do so (4). When these conditions are met, it is called "appropriate off-label use".

The Thalidomide Tragedy and its Impact on OLDU: Whenever we hear OLDU, we are reminded of the chilling thalidomide tragedy of late 1950s and early 1960s. Thalidomide was first introduced in West Germany by Chemie-Grünenthal as Contergan as an over the counter (OTC) sedative or hypnotic or anxiety reliever (5). Due to its anti-emetic effect, thalidomide soon found a wider OLDU

in morning sickness. However, its unrecognized teratogenic effect resulted in the birth of over 10,000 infants with phocomelia, a condition with malformation of limbs, in West Germany, Great Britain, Canada, and other countries, where the drug was available in pharmacies (6. 7). Fortunately, thalidomide was not approved by the US Food and Drug Administration (FDA) for use in the United States. But in the 1950s about 20,000 Americans were administered thalidomide as part of two clinical trials operated by the American drug makers Richardson-Merrell and Smith, Kline & French. This prompted the FDA to send an urgent warning to all its field officers and inspectors in 1962. These officers interviewed every doctor involved in the clinical trials or who had access to thalidomide to discover birth of deformed babies. It turned out at least 207 pregnant women participated in clinical trials of thalidomide in the United States, resulting in the birth of 17 deformed infants (8). On Aug. 1, 1962, President John F. Kennedy issued a warning: "Every woman in this country, I think, must be aware that it's most important that they check their medicine cabinet and that they do not take this drug" (9). Much credit goes to Frances Oldham Kelsey, a drug reviewer in the FDA, who adamantly stood between thalidomide and the American people by repeatedly refusing to approve the drug as it lacked rigorous safety data even before the thalidomide tragedy broke out (10). The pharma industry resubmitted their applications to the FDA six times with amendments. But Ms. Kelsey's professionalism and strong conviction stopped thalidomide from entering into the United States pharmacies and thus saved many thousands of American infants before the tragedy exploded in other countries. Later Ms. Kelsey received Presidential Award for distinguished service for not allowing thalidomide to be approved for sale in the United States (11).

Interestingly, despite its infamous history, in 1998 thalidomide was approved by the FDA for a variety of clinical uses (12). And thalidomide is listed in the World Health Organization's list of essential drugs (13). For some of these conditions, thalidomide received an "orphan drug" designation by the FDA (see below for more on orphan drugs and off-label use). As one can see later in this review, the anti-inflammatory properties of thalidomide helped it to resurrect as a possible treatment for COVID-19, including two registered clinical trials (NCT04273529; NCT04273581).

Today, the world is much safer and such grave tragedies do not happen thanks to the stringent criteria for drug safety evaluation by the FDA and its counterparts in other countries. The thalidomide disaster awakened the regulatory agencies in many countries prompting them to introduce tougher rules for testing, validating, and approving of drugs (8, 14). These include the Kefauver Harris Amendment in the United States (15), Directive 65/65/EEC1 in the European Union (16), and the Medicines Act 1968 in the United Kingdom (17). In the United States, the new regulations required applicants to disclose all side effects encountered in testing besides proving the efficacy of the drug. The FDA went on further reclassifying drugs already in the market through its Drug Efficacy Study Implementation (DESI) (18).

Scientific Aspects of OLDU: Besides off-label use of licensed drugs, there are unlicensed drugs, often called "off-licensed drugs" (19). These are common in countries such as the United Kingdom, but not in the United States. These are drugs not licensed by the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom, where physician's offices or pharmacies may compound medicines. These fall into five categories: i) extemporaneous dispensing; ii) pharmaceutical specials; iii) imported medicines licensed in other countries; iv) "Named Patient" supplies; and v) chemicals not licensed for human use. It should be noted that long before the advent of pharmaceutical companies most medicines were compounded from chemicals in the doctor's office or local apothecaries using *materia medica* as the recipe book. This age-old practice can be still seen in many countries.

Off-Label vs. Off-Target Effect: Having defined off-label use, let us examine the off-target effect. For example, when we treat a mixture of healthy and cancer cells in vitro with an anti-cancer drug, if the drug affects only the cancer cells but not the healthy cells, it is free from the off-target effect. But if the anti-cancer drug affects the healthy cells also besides cancer cells, then it has an off-target effect. In the former case, the anti-cancer drug may not have side effects when administered to patients. But in the latter case, the drug will manifest adverse effects in cancer patients. Thus, off-label refers to use, and off-target refers to effect. An off-label use can be due to an on-target or off-target effect. An off-target effect can be a beneficial off-label use or an adverse effect. Sometimes, the off-target effect may be predominant and overrides the on-target effect, and thus may be very useful in certain conditions (20).

In the past off-target effect was considered as unwanted property of a drug resulting in drug toxicity. However, advances in protein chemistry, molecular

biology, population genetics, epigenetics, target fishing, and computational-based approaches changed that view. Today, off-target effects of drugs are being exploited as tools to develop multi-target drugs that will help in treating complex and often intractable diseases, such as cancers, neurodegeneration, malaria, and tuberculosis among others (21-27). These developments in turn are leading to polypharmacology as against polypharmacy.

Off-Label Use is Very Common: OLDU is very common in real world clinical practice (28-30). In an analysis of 725 million prescriptions conducted by the Stanford University, it was found that 21% were for OLDU. Of these, only 6% had scientific evidence, whereas the rest 15% were prescribed with no scientific basis (cited by The Pharmaletter, 2006). The most commonly prescribed OLDU were for anticonvulsants, cardiac medications, anti-asthmatics, and allergy therapies. The least off-label prescriptions were found among anti-diabetic and anti-hypertensive drugs, lipid lowering agents, and analgesics. The rest of the medications fall in between. Thus, OLDU is more common in diseases influenced by the heterogeneity of patient outcomes (e.g., psychotropics). Analysis of off-label prescribing among office-based physicians using the National Disease and Therapeutic Index (NDTI) database from the year 2001 for 160 commonly prescribed drugs revealed the following. About 150 million off-label prescriptions account for 21% of overall prescriptions. The most common off-label prescriptions were for cardiac medications (46%, excluding anti-hyperlipidemic and anti-hypertensive agents), and anticonvulsants (46%). Gabapentin (83%) and amitriptyline hydrochloride (81%) showed the highest proportion of off-label use (21). Those that are at the higher end of the spectrum of off-label use also have a low proportion of scientific basis.

Off-Label Use and Adverse Drug Events: Published studies show that OLDU is associated with significantly higher cumulative hazard ratios (HRs) of adverse drug events (ADEs) as compared to on-label use of drugs. (31). It is interesting when the OLDU was split into two groups, those with scientific basis and those without scientific basis, the HRs of ADEs with scientific basis were not different from those of on-label use of drugs (31). Thus, off-label use without a scientific basis is a risk factor for adverse drug events.

Facts about Off-Label Use: There are a few facts about OLDU: i) both prescription and OTC (over-the-counter) drugs can be used as off-label; ii) OLDU is the most common in anticonvulsants, with 73% having little or no scientific basis; iii) some drugs are used more frequently off-label than for their original approved indications (e.g., tricyclic antidepressants for neuropathic pain or ADHD or attention deficit hyperactivity disorder).

Clinical Usage of Off-Label Drugs: The clinical usage of off-label drugs is diverse and is often dictated by need and lack of choice, but not necessarily by rational science or evidence-based clinical outcome.

Motivation behind OLDU: This involves factors related to physicians, patients, and drugs. Pathophysiology of condition being treated by a physician could be the same or close to the approved indication by the FDA. This is more common in cancer patients. If a targeted therapy is approved in a particular cancer, oncologists tend to use that targeted therapy in other cancers where the same target might be involved (examples include use of HER2, BRAF, PI3K inhibitors, and PARP inhibitors). Another common situation would be an anecdotal experience with great success in a small cohort of patients. For example, use of aspirin prophylaxis for coronary disease in high-risk patients is an off-label use. But it is widely accepted by primary care physicians and cardiologists. Furthermore, when the best possible therapeutic agent fails, the patient may demand new treatment which may be off-label use. There are also monetary factors involved in OLDU that benefit the patients.

Obstetrics: OLDU is very common in obstetrics. Due to the small market size, and high risk of medicolegal actions, the pharma industry is discouraged to produce new drugs for obstetrics. It is unethical to conduct randomized placebo-controlled trials in pregnant women. The thalidomide tragedy resulted in FDA excluding women of childbearing potential from clinical trials of new drugs until 1993. So, drugs used in obstetrics were originally studied in non-pregnant women or pregnant animals. Hence, direct extrapolation of results to pregnant women is not right always. Because of these, and due to the absence of specific guidelines, obstetricians are forced to take tough decisions for off-label use of available medicines (32). It was only after 2009 FDA has started a systematic study of the outcomes in women who had taken prescription drugs during pregnancy. In recent years compelling reasons, such as it is prudent to gather evidence from fewer pregnant women and their fetuses under rigorously controlled scientific conditions than exposing much larger numbers later in the market are being put forward (33).

Pediatrics: OLDU in children is very common, up to 79% in hospital set up and 56% in the community practice (34-36). Many drugs in children are used based on trials conducted on adults. The Pediatric Research Equity Act 2003 gave FDA the authority to require pediatric studies in certain drugs and biological products with a goal to obtain pediatric labeling for the products (37). In 2014, the American Academy of Pediatrics declared: *Evidence, not label indication, remains the gold standard from which practitioners draw when making therapeutic decisions for their patients* (38). Besides these, ethical issues may arise when children above 7 years old do not comply with informed consent given by their parents and assent or dissent on their own. As compared to adults, children and infants have larger body surface area relative to their body weight. So, the pharmacokinetics and pharmacodynamics, and metabolism of drugs in children differ from those in adults. Children's kidneys cannot cope up with stressful conditions, such as nephrotoxic medications. Hence, one has to be careful while determining the doses for OLDU in children.

In recent years, the OLDU of a drug in infants and children prompted FDA to regulate its usage. Originally approved for erectile dysfunction in men, sildenafil, a phosphodiesterase-V inhibitor, quickly found OLDU in pulmonary arterial hypertension (PAH), a debilitating condition with a risk of mortality in infants and children with diverse cardiac, pulmonary, and systemic diseases (39, 40). However, the safety and ethics in using sildenafil in infants and children was questioned (41, 42). Despite extensive clinical experience and approval by the European Medicines Agency (EMA), FDA has issued a warning for sildenafil for use in pediatric PAH between 1 and 17 years of age due to an apparent increase in mortality during long-term therapy. These restrictions by FDA prompted the pediatric physician community to use lower doses of sildenafil and frequent monitoring of their patients and to conduct more controlled studies (43). This is an example where FDA can intervene in off-label prescribing by physicians when drug safety is a concern.

Cancers: OLDU is very common in cancer patients. The prevalence of OLDU is about 18 to 41% in cancer patients (44). Most of the OLDU is seen in patients with metastatic cancer and in need of palliative care. Lack of options also dictates OLDU in cancers. Many anti-cancer agents are effective in more than one type of cancer. Some cancer patients have limited response to approved drugs. FDA approves the use of individual cancer drugs, but it does not approve combination of drugs or regimens. So, using a combination of approved drugs in cancer patients is technically off-label (44).

Geriatrics: Geriatric medicine is a challenging area for physicians. Most clinical studies in adults are limited up to the age of 65 years. Geriatric patients have chronic diseases that alter drug tolerance, pharmacokinetics (PK), and ADME (absorption, distribution, metabolism, and elimination) of drugs. Polypharmacy is also common among this demographic, due to which lack of compliance is a problem. Gradually decreasing renal function in older patients predisposes them to nephrotoxic drug reactions (45, 46). Due to these facts, there is a knowledge gap in labeling and use of drugs in geriatric patients (47). This may dictate the physicians to start with lower doses of drugs in geriatric patients and titrate the dose gradually upward, especially when using off-label drugs.

Palliative Care: In acute palliative care units, about 1/3rd of drug usage is off-label (48). This use has clinical, ethical, and legal implications (49). Mixing two or more licensed drugs in an intravenous infusion for continuous administration, a standard practice in palliative care is officially an unlicensed preparation. Research needs to establish the iatrogenic effects of off-label use in palliative care. More than half of the prescriptions in pediatric palliative care units (PPCU) are off-label or unlicensed uses (50). Of concern is the traditional view of illness is changing in palliative care with the emerging disease-specific trajectory, which further complicates off-label use of drugs (51).

Physician Aspect of Off-Label Use:

There are several issues with off-label use which the physicians must know. A provider may encounter ethical and legal questions while prescribing off-label use of drugs.

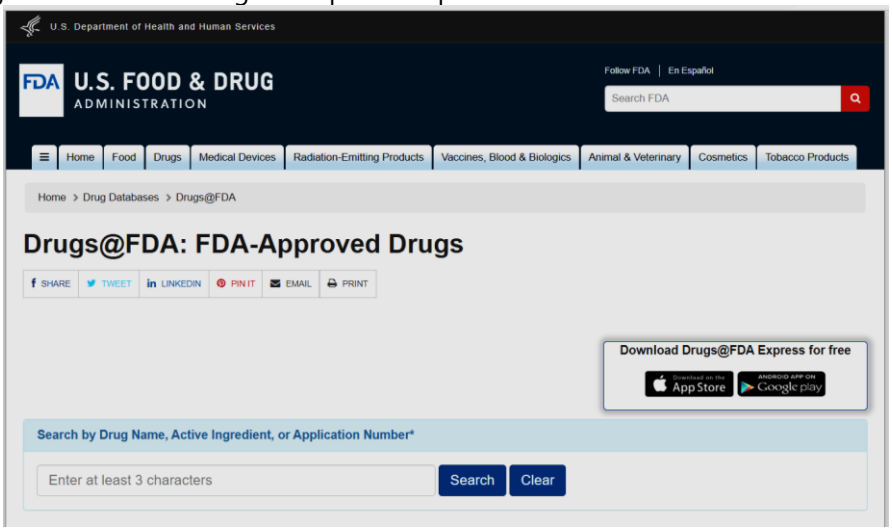
Ethics vs. Legality: When an OLDU causes an injury, the patient may sue the physician for lack of informed consent or for negligence. Lack of informed consent per se does not win the case in the court for the patient (52). It is because courts do not require physicians to disclose OLDU to their patients. It is a matter of legal judgment, and it is not based on ethics. United States Supreme Court declared that physicians can prescribe approved items for any use they deem reasonable. But institutes or hospitals or medical schools or Veterans Affairs Medical Centers where the physicians work may have their own code of conduct and ethics on informed consent, which may go beyond legal definitions. What is legal and what is ethical may not be the same. While a physician may be cleared legally in a

court for OLDU without informed consent, it is not necessary that his/her own institute will clear ethically and may take disciplinary action. Finally, physicians should know off-label marketing by pharmaceutical companies has been one of the most common causes of Medicaid fraudulent claim investigations (53, 54).

Negligence: Off-label prescription per se does not constitute a liability. So, establishing negligence needs to show that the provider has deviated from the standard of practice. Standard of practice is defined as wider use, supported by peer-reviewed publications and in good faith (52). Here comes the importance of having a scientific basis for off-label use of drugs. Fortunately, until now all cases of negligence targeted at OLDU by providers were dismissed by the courts. But as the number of lawsuits related to OLDU increases substantially thanks to their promotion by electronic prescription machines (see below), we cannot expect that courts will ignore negligence related to off-label use.

FDA and Physicians: FDA does not hold physicians accountable for off-label prescribing. But FDA will investigate if a physician crosses the fine line between "treatment" and "research" (55). The goal of treatment is to provide diagnosis, preventive care, and therapy. The goal of research is to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalized knowledge. If a provider prescribed off-label in the research context and advocates it to his/her colleagues through lectures or podcasts or blogs or other means, then FDA considers that as research. In such a case, that activity should comply with the FDA and institutional regulations for conducting clinical research. So, by crossing the line between treatment and research, a physician comes under the radar of the FDA and regulatory agencies. However, lecturing on OLDU in accredited Continued Medical Education (CME) programs with proper disclosure as per the requirements of the American Medical Association, such as *all clinical presentations should be based on evidence accepted within the profession of medicine* is exempted from FDA scrutiny.

Empowering and Protecting Physicians: Physicians can empower and protect themselves by following a few simple steps as follows. ***i) Continued Medical Education:*** This allows the dissemination of the most credible knowledge in the best interests of the patients; ***ii) Obtaining Informed Consent:*** Physicians have an ethical duty to disclose the facts material to their patient's treatment decisions, and patients have a right to know any inherent risks; ***iii) Record Keeping:*** All off-label prescribing should be backed up by scientific evidence, citations, and conversations with the medical community members and with patients. This includes documentation of continued medical education as well;



iv) On-Label Search: It is a good practice to check the FDA approved uses for a drug by going to the FDA website by typing the following in the web browser:

https://www.accessdata.fda.gov/scripts/-cder/daf.

One will see the adjacent page. Enter the name of the drug (generic or brand name) in the search box at the lower part of the screen and hit the search icon. This should give details for FDA approval for a drug. If the use one intends to prescribe is not listed there, then it is an off-label use.

In such a case, one should search for any available scientific evidence for the intended use. For that one should type the following in the google search box and check. For searching OLDU, Google is preferable to PubMed. PubMed search is limited to the journals successfully registered with the National Library of Medicine (NLM). Conversely, Google search can find information from both PubMed indexed and non-indexed journals, meeting abstracts and proceedings, unpublished scientific reports, thesis abstracts, books and all such sources. The algorithms of Google also allow searching by a combination of key

words. Thus, Google search for OLDU is exhaustive and very helpful.

If there is any piece of scientific evidence from human or animal studies, Google will display that. One should review those pages and print them and file those in the patient's records as a backup for defense if a dispute arises. Even a little bit of scientific evidence helps a lot more than no scientific evidence. This also gives an impression in the court that the physician was scientifically inclined and was thorough. Although judges go by objective evidence, they do give credit for thoroughness and genuine attempts by providers to help their patients.

Electronic Prescribing and Promotion of OLDU: In recent years commercial Electronic Health Records (EHR) and Electronic Prescribing have become common in large hospitals and teaching hospitals and institutes. They do have certain advantages, such as prevention of prescription errors, streamlining coding and billing by interfacing them with prescription, and thus reducing the burden on providers and hospital staff, and accounting departments. But they do have caveats and negative outcomes. These electronic prescription systems are supposed to have only FDA-approved indications for drugs in the pull-down menu on the screen. But, they are also loaded with unapproved off-label indications. For example, in one commercial electronic prescription system, 13 indications for atorvastatin were listed, whereas FDA approved only 10. Prevention of transient ischemic attacks, an unapproved indication was listed, whereas 3 approved indications with a major impact on patients and health care costs are not on the list (56). Unlike the pharma industry, these electronic prescribing systems are not regulated by the FDA. So, apparently, they are becoming de facto sales representatives of the pharma industry influencing physicians, particularly those in training and residents. This raises a critical question: *Who decides what is included in an EHR drug information module, and how are those decisions made?* (57). Ideally speaking, FDA should regulate the prescription programming of EHR. However, that hope was struck off in August 2017 by the US Court in *Amarin vs. FDA* by handing down a ruling that the *US Food and Drug Administration lacked the authority to prohibit non-misleading forms of off-label speech* (57). This is a wake-up call for all physicians who would like to promote evidence-based medicine and reduce adverse drug events to police their own prescription practices. So, the onus of correcting this anomaly lies on the shoulders of senior physicians by systematically screening these machines and getting the unapproved uses deleted. Thus, it is imperative that institutional oversight is required for electronic prescribing systems. Finally, a national random sample mail survey of physicians conducted in 2007 and 2008 highlighted the dire necessity for effective methods to inform physicians about the evidence base, or lack thereof for drugs they prescribe off label (58).

Reimbursement and Coverage for OLDU : Medicare Part D covers drugs prescribed for off-label use only if the drugs are identified as safe and effective for that use in one of three officially recognized drug compendia (59). Compendia and drug information reference handbooks are published by organizations or companies independent from drug manufacturers. These references typically include information on both labeled and off-label uses. Medicare, Medicaid, and many major private insurers cover off-label uses if they are included in major compendia, such as the American Hospital Formulary Service Drug Information (AHFS DI), the U.S. Pharmacopeia Drug Information (USP DI), and/or Drugdex (60). However, in some specialties, such as dermatology, the treatment options in compendia are incomplete, outdated, idiosyncratic, and unpredictable (61). Thus, by statute, Medicare is obligated to cover drugs used for a "medically accepted indication" as defined by compendia. However, in a legal battle *Layzer (Patient) v. Leavitt (DHHS)*, the physician ordered drugs with recognized support in the medical literature, but not in the compendia, which resulted in denying payment by Medicare. Observing that FDA-approved uses often lag behind the knowledge of actual effective treatment, the court ruled that consistent with FDA's published advisories, "medically accepted indications" can include off-label use (62).

FDA and Pharma Industry: The 1938 Food, Drug and Cosmetic Act gave the FDA the power to regulate promotional materials on medications. The 1997 FDA Modernization Act allowed manufacturers to distribute to health care providers peer-reviewed journal articles about unapproved uses of medications. Pharma industry repress-

entatives whispered both published and unpublished off-label uses of their drugs to healthcare providers. FDA objected to this practice, resulting in the pharma industry suing the FDA. The court gave a judgment that FDA could not "prohibit the truthful promotion of a drug for unapproved uses because doing so would violate the protection of free speech". This is the first time the First Amendment Right was invoked in a legal dispute over OLDU (62). This may have wider implications for the promotion of off-label use by the pharma industry.

To officially convert an off-label use as on-label use, the pharma industry has to spend substantial money by conducting efficacy and safety studies for the new uses. There is no financial incentive for the pharma industry to do so, especially if the patent expired and the drug in the market is generic. Furthermore, the FDA gives barely 3 years exclusivities to the pharma industry to add additional indications to their drugs, which is not sufficient time period. Marketing strategists do not like to reposition their flagship drugs to protect the revenue and stock price of the company. *The above issues make OLDU the art and science of the health care providers, leaving the use of drugs off-label forever.*

However, the FDA and the Department of Justice have been aggressive in going after pharma companies that openly advocated or promoted OLDU for their approved drugs. Here are examples, showing heavy penalties the pharma companies paid.

Company	Relevant Drug	Year	Penalty
Warner-Lambert	Gabapentin	2004	$430 million
Eli Lilly	Olanzapine	2009	$1.415 billion
AstraZeneca	Seroquil	2010	$520 million
Novartis	Six Drugs	2010	$423 million
Amgen	Aransep	2012	$762 million
J & J	Ripersdal	2012	$181 million
GaxoSmithKline	Paroxetine	2012	$3 billion
	Bupropion		

Despite these heavy penalties, courts do not agree that it is a lawful government effort to regulate commercial enterprises.

Economic Impact of OLDU: If scientifically established, off-label use of existing drugs is not only a boon to the medical profession but also has a marked impact on healthcare costs. In view of this, in 2017 Arizona became the first state to allow the pharma industry to promote "truthful off-label use" of their products by its Free Speech in Medicine Act. This was followed by the enactment of a similar law by Tennessee in 2018. Other states may follow the suit, as this will benefit the healthcare systems of those states. Supporters say it makes sense to get rid of restrictions on off-label uses when there is plenty of information and evidence available. Critiques say that rampant use of questionable off-label uses encouraged by the pharma industry leads to substantial patient morbidity and mortality. Academicians and experts say that unregulated widespread use of OLDU can potentially erode the base of evidence-based medicine. Until now the FDA remained silent on Arizona or Tennessee off-label use laws. But FDA may likely tighten its grip on the "safety" issue, the only weapon it can legally use to contain states and to counter First Amendment Right. Just because a drug is safe in an approved disease condition does not mean it is also safe to administer in an unapproved disease condition. With diseases, drug safety is relative.

Right to Try Act: In 2017 the United States Congress enacted *Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act* (63). This law allows physicians to administer experimental drugs to terminally ill patients after exhausting all approved treatment options. Under this Act, the physicians can obtain the experimental drugs directly from the drug manufacturers without the involvement of the FDA. However, the experimental drug must have undergone FDA's Phase I (safety) testing, and the drug manufacturers are not legally mandated to provide the experimental drugs to patients under this Act.

Orphan Drug Act and Off-Label Use: After intense lobbying by the National Organization for Rare Disorders (NORD), in 1983 the United States Congress passed the Orphan Drug Act (ODA) (64). The ODA grants special status to a *drug* or biological product targeting a rare disease or condition, which affects a few patients, such as Gaucher's disease, Tourette's syndrome, Huntington's disease, myoclonus, Amylotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease), combined immunodeficiency (SCID), and certain types of cancers. Because of the small number of patients affected, pharmaceutical companies do not see incentive in developing new therapies for them. The law provides three incentives to pharmaceutical companies: (i) 7-year market exclusivity to sponsors of approved orphan products, (ii) a tax credit of 50% of the cost of conducting human clinical trials, and (iii) Federal research grants for clinical testing of new therapies to treat and/or diagnose rare diseases (65).

Although the Congress enacted ODA with good intention to foster innovation, unfortunately the pharma

industry has been taking advantage of it to pad its profits margins. Drugs originally approved through ODA, are subsequently marketed for off-label use in other disease conditions which are not rare, thus boosting the profits within a short span (66). The estimated global market for orphan drugs in 2019 was US$ 147.56 billion. It is expected to grow at a CAGR (Compound Annual Growth Rate) of 10% to reach $413.billion by the year 2030. Since multiple FDA approvals boost the stock prices, pharma industry found an easy way to boost their stock prices by filing approval for orphan drugs. Obviously, Congress needs to enact new laws to check abuse of ODA.

Unsolved Problems: Despite all concerned parties expressed their views, the OLDU remains like unchartered territory. Both the pharma industry and states want to promote off-label use because of economic benefits to them. Although FDA is concerned about safety, it is not willing to step in and regulate OLDU. In addition, the FDA is short on resources and trained personnel. Physicians have the freedom to decide, but their hands are tied with reimbursements, and potential lawsuits by their patients. In addition, there is a clear knowledge gap in the physician community with the scientific basis of off-label prescriptions they write routinely. Academicians think unregulated rampant prescriptions for off-label use without scientific evidence will erode evidence-based medical practice. In recent years the stakes have gone up due to introduction of electronic prescription systems which have no FDA oversight or legal controls.

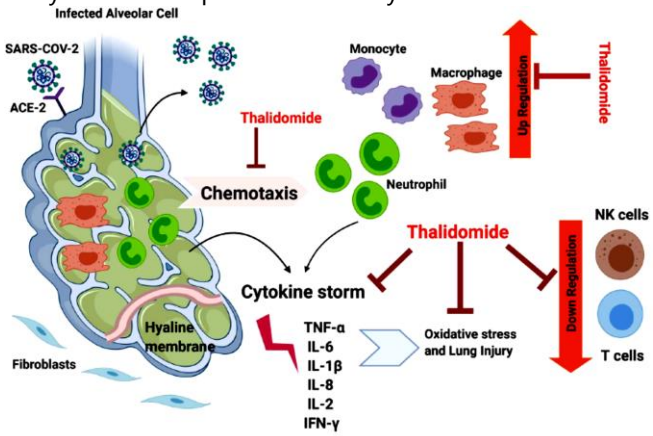


Figure 1: The theoretical efficacy of Thalidomide in attenuating the inflammation associated with COVID-19. Lungs infected by SARS-CoV-2 possess suppressed immune response, elevated inflammation, activated cytokine storm, and excessive oxidation stress leading to lethal lung injury. Thalidomide could potentially inhibit chemotaxis of neutrophils and suppresses them along with that of monocytes. It could possibly downregulate the cytokine storm by acting on several involved factors and can suppress independently the associated oxidative stress. Thalidomide is also known to be an up-regulator for NK and T cells and thus can reverse the downregulatory effect of COVID-19. (TNFα, Tumor necrosis factor alpha; IL, interleukin; ACE-2, Angio-tensin-converting enzyme 2; IFN-γ, Interferon gamma).

Figure and Legend reproduced from Khalil et al, Frontiers in Dermatology 2020 (67). Open Access Creative Commons Attribution License (CC-BY)

OLDU in COVID-19: The SARS-CoV-2 pandemic is witnessing an unprecedented rise in OLDU in a desperate attempt to prevent or treat COVID-19. Several publications appeared on drug repurposing in COVID-19 with a long-list of potential medications (67-71). While some have potential theoretically, very few are tested scientifically. And even among those tested scientifically, the results or outcomes are variable or not as expected. Perhaps the most promising OLDU in COVID-19 has been with the corticosteroid dexamethasone with a reduction in death rate up to 33% in hospitalized COVID-19 patients with severe respiratory complications. To some extent, the failure of other drugs in COVID-19 is due to our being on a steep learning curve in understanding the myriad manifestations of COVID-19. Even those drugs registered for clinical studies may take a long time to generate any meaningful data, perhaps only after the pandemic has receded. So, as early as March 31, 2020, the World Health Organization has issued the following statement in its Scientific Brief: *It can be ethically appropriate to offer individual patients experimental interventions on an emergency basis outside clinical trials, provided that no proven effective treatment exists; it is not possible to initiate clinical studies immediately; the patient or his or her legal representative has given informed consent; and the emergency use of the intervention is monitored; and the results are documented and shared in a timely manner with the wider medical and scientific community* (72).

Ironically, after reported positive outcome in a patient treated with thalidomide along with other drugs, two clinical trials have been registered to evaluate the efficacy of thalidomide in COVID-19 (NCT04273529; NCT04273581). Thalidomide has FDA approval for treating erythema nodosum leprosum (ENL), and multiple myeloma (MM), and it is believed that it may also work in the severe respiratory syndrome of COVID-19. As shown in

the following figure, theoretically thalidomide has potential therapeutic benefits. But whether it works in COVID-19 or not can be inferred from the ongoing clinical studies only. Even if it works to some extent, the major limitation in the widespread use of thalidomide in COVID-19 is limited clinical experience with the drug (67).

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Focused Review Article

Post-Traumatic Stress Disorder: Possible Neural Networks Facilitating Neuromodulation in the Management

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Abstract: Post-Traumatic Stress Disorder (PTSD) has an estimated lifetime prevalence of 7% in the United States, especially in combat-veterans. In a 2008 study, the cost of PTSD management was $6.2 billion. In its severe form PTSD reduces quality of life significantly resulting in personal, social and financial losses leading to substance abuse and suicidal tendency. It has a 17% death rate during a 6-year follow up in combat veterans. Studies failed to identify the reasons some people are prone to develop PTSD while others recover from traumatic episodes. Functional neuro-imaging techniques demonstrated the responsible neural circuits involving the amygdala, hippocampus, prefrontal cortex, and other projections from the mesial temporal lobe. At present, treatment consists of medical management, psychotherapy, prolonged exposure therapies (PE) and cognitive processing therapy (CPT) with proven efficacy. However, PTSD remains refractory in people with severe trauma, chronic exposure to trauma, and co-morbid conditions like psychiatric illness or substance abuse. It is also possible these conservative treatments fail to abolish the activity of neural circuits responsible for the anxiety components. In animals, deep brain stimulation (DBS) of the amygdala and its projections effectively suppressed anxiety, fear extinction and other components of PTSD, thus supporting the neuroimaging findings of the neural networks engaged in the pathophysiology of this disease. The first patient with refractory combat PTSD who received DBS of bilateral amygdala belongs to an ongoing clinical trial, and over several months follow up exhibited continued improvement in symptoms like sleep pattern, anxiety, and dissociative episodes. Another case series of two PTSD patients with refractory mesial temporal lobe epilepsy underwent LASER amygdalo-hippocampotomy that abolished the patients' intractable PTSD symptoms as well. Currently, apart from DBS, non-invasive approaches like focused ultrasound, stimulation with magnetic/electrical energy and infrared laser appear promising in neuromodulation of this difficult disorder.

Key Words: PTSD; Combat-Veterans; Deep Brain Stimulation; Psychotherapy; Amygdala; Hippocampus; fMRI

Introduction: Post-traumatic stress disorder, a devastating neurological disease, is currently receiving attention long overdue. Combat PTSD has been reported to have a life-time incidence of 6.8% and prevalence of 3.5% in 12 months (1, 2). Original combat PTSD following military trauma is higher in veterans as reported in a 1990 survey of Vietnam War veterans; more in men compared to women (3). Similarly, 12.1% of Gulf-War veterans had a PTSD diagnosis (4) almost akin to (13%) Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans (5). The cost of PTSD management was reportedly $6.2 billion in a 2008 study on the Iraq and Afghanistan

veterans (6). PTSD in its severe form affects quality of life significantly, leading to unhappiness, depression, and marital dysfunction (7-9). It can lead to inability to work, substance abuse, worsening of general health and suicidal tendencies (10-13). Onset of psychotic features warrants the worst form of PTSD (14). Even with aggressive interventions, PTSD was reported to cause 17% of deaths during a 6-year follow up of combat veterans at the National Center for PTSD (NCPTSD), New Haven, CT (15). It is unclear how and why some people develop PTSD while others remain resilient and recover from the traumatic episode. In one North American cohort study a lifetime estimate of 60-80% was recorded regarding any exposure to a traumatic event capable enough to result in PTSD; but only 10-30% had exhibited PTSD features (16).

At present, evidence-based treatment of PTSD consists of medications and/or psychotherapy. The former consists of selective serotonin reuptake inhibitors (SSRI) antidepressants and individual or group psychotherapies. Prolonged exposure therapies (PE), cognitive processing therapy (CPT) and eye movement desensitization and reprocessing (EMDR) (17-19) are the other evidence-based therapies with proven efficacy. Deep brain stimulation (DBS) is a rapidly expanding field of neuromodulation with an increased number of indications for many psychological diseases, besides movement disorders. Obsessive-compulsive disorder (OCD), depression, anorexia and addiction are among the several other conditions undergoing clinical trials (20-24). Improved knowledge regarding the neural circuits and functional imaging of the brain (human connectome) may provide a strong morphological basis for neuromodulation in PTSD, hopefully a successful intervention for this intractable condition with dismal prognosis.

Neural Network in PTSD: Cerebral localization work starting in the laboratory of Victor Horsley in late 18th century, continued by several others in Europe and the Americas, provided valuable information to elucidate multiple previously unexplained neuropsychological conditions (25, 26). Many investigations into the neurological substrate for PTSD have been useful in providing much needed information to improve the management of this condition.

Etiology and Pathophysiology: Similar to other psychological disorders, PTSD also demonstrated a genetic predisposition and a positive correlation with other risk factors such as poor social/family support, childhood trauma, and family history of psychiatric illness (27-29). Additional correlation was identified with genetic polymerphism, endocrine dysfunction, abnormal neurotrophic factors and neuropeptides/neurotransmitters (30-34).

Anatomical Substrate: Rodent models, in laboratory studies, demonstrated similarities between their fear processing neural circuits and PTSD (35). Recent advancement with magnetic resonance (MR) imaging techniques including the fiber tract imagery, human connectome project and functional MR demonstrated several important causative structures for PTSD. Previous animal experiments demonstrated the role of the medial temporal lobe structures like amygdala, hippocampus and their connections in developing neuropsychiatric syndromes (36-38).

Functional MR and advanced neuro-imaging techniques demonstrated that the anatomical substrate for fear conditioning engaged amygdala, hippocampus, and prefrontal cortical projections via the thalamus. Earlier work by Kluver and Bucy, followed later by Aggleton and Passingham (39-40) demonstrated the importance of temporal lobe structures, especially the amygdala, in neuropsychological manifestations in monkeys. More refined examination of the amygdala connections reveal that fear conditioning can be successfully diminished by ablation of the basolateral complex (41). Cortical projections from amygdala nuclei elicit other autonomic reflex actions of fear (42).

But circuits for fear extinction engage the ventromedial prefrontal cortex, amygdala (basolateral complex, intercalated cell cluster) and the hippocampus where, plasticity of amygdala gets modulated by medial the prefrontal cortex (Figure 1) (43-44). In experimental studies, animals had utilized GABAergic neurons for fear extinction in the amygdala, based on output from the basolateral complex (45). In humans with PTSD, several imaging studies including fMRI, single-photon emission tomography (SPECT), positron emission tomography (PET) demonstrated alterations in blood flow in the neural circuitry involving the amygdala, hippocampus and prefrontal cortex during tasks and at rest (46, 47). Additionally, the insular cortex and dorsal anterior cingulate cortex became hyperactive (48). Severity of symptoms in anxiety disorders, PTSD and some phobia related conditions was correlated with reduced activity in the inferior occipital gyrus, ventromedial prefrontal gyrus, para-hippocampal gyrus, lingual gyrus, putamen and other cortical areas in functional imaging studies (Figure 2) (49).

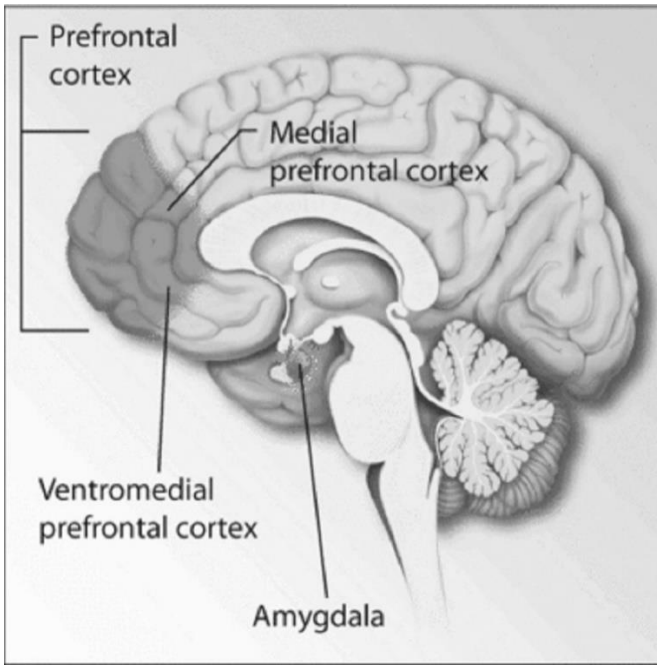

Figure 1: Neural components involved in PTSD pathoph ysiology. (Courtesy: Creative Commons. CC BY-SA 3.0)

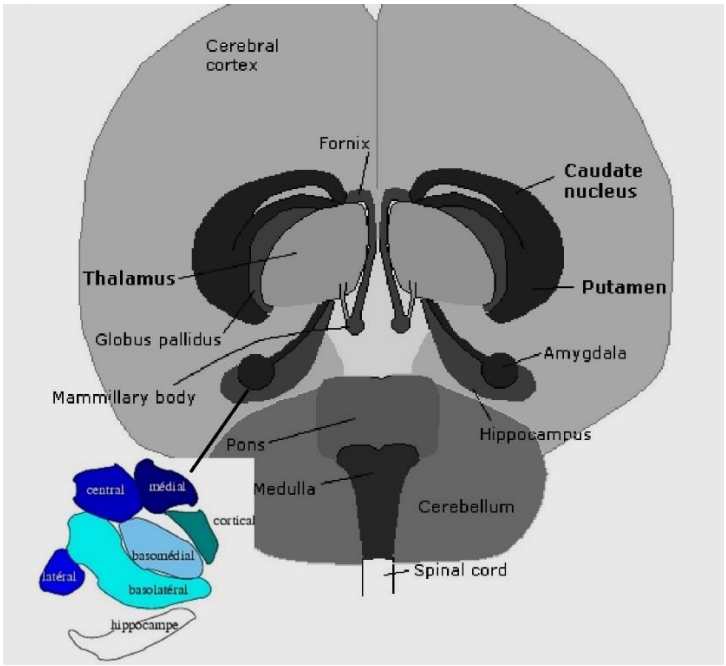

Figure 2: Amygdala and its components (Courtesy: Creative Commons. CC-PD-MARK/NIH images).

Neuromodulation by Deep Brain Stimulation (DBS): In animal models several targets were stimulated based on the experience gained in studies as above. These models provided targets like the amygdala, hippocampus, striatum or cortical areas.

Amygdala (Basolateral Component-BLA): In PTSD rat models, Langevin et al reported a therapeutic response in terms of reduced hyperactivity in the amygdala when DBS was given to BLA 50-51). This experience was clinically applied in combat veterans with PTSD in 2014 and is being studied by the same group in an ongoing clinical trial. PET scans (18F-fluorodeoxyglucose) were obtained to record the metabolism in the amygdala before stimulation, at rest, and during an activated state. Patients also had video-electroencephalograms after DBS electrodes were placed. Safety of the procedure was recorded, and early reports suggest clinical improvement. In one of the combat-veterans with a DBS implanted for his refractory PTSD, clinical improvement was noticeable at eight months postoperatively with a 37.8% reduction in CAPS (Clinician applied PTSD scale) scores compared to baseline scores (52-53).

Hippocampus: To abolish fear extinction, the hippo-campal projections to the medial prefrontal cortex were stimulated in rats and recall of memory extinction was successfully reduced (54). Similarly, DBS of ventral striatum or medial frontal cortex in rat models had shown promising results in altering fear extinction (55, 56).

Deep Brain Stimulation: Role in PTSD: In 1963, utility of DBS was reported for the first time by Bekthereva from Leningrad's Institute of Experimental Medicine and the Academy of Medical Sciences (57). This was followed by Benabid's report of DBS for movement disorders using long term high-frequencies for stimulation as well as ablative procedures in 1987 (58-60). Within a short while DBS became a successful procedure to manage movement disorders. Approval was given by the FDA in the United States in 1997 for essential tremor and later for tremor related to Parkinson Disease targeting thalamic locations. Then in 2003, approval was given for DBS of subthalamic nucleus and globus pallidus interna. It was only in 2009 that DBS got permissions for usage in psychiatric diseases like obsessive-compulsive disorder (61). Several other neuropsychiatric illnesses (bipolar disorder, schizophrenia, addiction) have been under trials since then; PTSD being one among them and the amygdala has support from preclinical evidence as a potential target.

DBS is currently an acceptable invasive neuromodulation technique in the management of movement disorders. It is an invasive surgical procedure, complications like hemorrhage and seizures are reported, although within an acceptable range (62, 63). Gippert et al observed that the response in patients with bipolar disorder (BD) managed with DBS, was similar to that of maniac-depression disorder (MDD) patients. These MDD patients had remission from depression with adjustable response correlating with stimulation parameters like frequency and duration of DBS (64).

DBS of Amygdala for PTSD: The first case of bilateral DBS of the basolateral amygdala was reported by Langevin et al; part of a clinical trial recently initiated. One patient with refractory combat PTSD received treatment with DBS of the amygdala and continued to show improvement over 8-month follow-up in symptoms like sleep, anxiety, nightmare frequency, dissociative episodes and tolerance (64).

Additional Targets and Procedures for PTSD: Recently Hamani et al reported their experience with a patient with refractory PTSD with DBS of medial prefrontal cortex (one of the anatomical substrates described above engaged in fear extinction) and uncinate fasciculus (66). It has been demonstrated there was decreased prefrontal inhibition of the amygdala in PTSD patients (67). With neuromodulation, the functional activity of this projection could be modified resulting in disruption of the inhibition. Bijanki et al presented the possibility of abolishing intractable symptoms of PTSD by LASER ablation of amygdala-hippocampus connections (68). In both cases, the patients presented with mesial temporal lobe epilepsy not responding to medical treatment. Both patients, following the LASER amygdalohippocampotomy on the right side, exhibited reduction in their seizures and also significant improvement in their PTSD parameters.

Discussion: In the United States alone PTSD has an estimated lifetime prevalence of 7%, especially involving combat veterans and males more than females (65, 69). With onset of new pharmacotherapy and psychotherapy methods, there have been many different treatments offered for PTSD management albeit with limited efficiency, predominantly due to their inability to control fear-extinction which gets modulated by the amygdala (basolateral nucleus) and medial prefrontal cortex as visualized on fMRI and other imaging modalities (72-73). These anatomical locations are at present accessible to neuromodulation and possibly effective targets to manage PTSD (73). Non-invasive and conservative methods of treatments include medical management with SSRI and SNRI (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors), cognitive behavioral therapy and prolonged exposure therapy (PE). Following PE therapy a 50% reduction in the symptomatology was observed in almost 50% of combat-veterans across the country after an average of 11.6 weeks of therapy (74, 75). In two other reports, Goodson et al and Tuerk et al reported similar beneficial effects of PE therapy (76, 77). SSRI treatment yielded about 60% response rates and following psychotherapy over 30% of patients continue to have PTSD symptoms (78, 79). Thus, treatment resistant PTSD continues to pose challenges and these patients are those with more severe symptoms with chronic exposure or multiple trauma and comorbid factors like substance abuse or preexisting psychiatric illness (MDD, anxiety, bipolar disorder, depression) (29, 80). This refractory nature of PTSD might be due to ineffectiveness of these treatments on the neural circuits responsible. Recent studies established connections between prefrontal cortex and amygdala playing active role in hypo or hyperarousal of negative emotions (81-83).

Amygdala projections have been shown to control emotional over/under-modulation as well as emotional numbing in clinical studies using fMRI (49, 84). Animal models suggested that DBS of the amygdala, hippocampus and prefrontal cortex effectively suppressed anxiety disorder and fear extinction thus, providing support to the fMRI observations regarding the neural circuits of PTSD (85). Translation of experimental observations into clinical practice always has certain limitations, in general and in particular, with PTSD, the models were not pretreated medically and DBS had limited stimulation parameters. Yet, the animal models provided useful information regarding the targets and the mechanisms involved (86). Additionally, "refractory PTSD" patients have limited options currently once the conservative measures are exhausted (87).

DBS has not only been effective in the management of movements disorders but currently is an established safe and effective procedure also. Recent trials demonstrate promising results supporting DBS for psychiatric disorders while the inclusion/exclusion criteria have been evolving (88-89). Such criteria for PTSD are yet to be established, especially in refractory patients with co-morbidities like psychiatric illness or substance abuse (80.

Summary: Literature on neuromodulation of PTSD has only sparse experience reported so far, that is nevertheless encouraging and clinical trials targeting the anatomical substrate are being explored. Identification of appropriate neural circuits, increased evidence regarding the patho-physiology, high resolution imaging of the targets, wider spectrum of DBS parameters and non-invasive monitoring incorporated into multicenter studies promise a better outcome for this disorder with dismal prognosis especially in refractory status.

Promising non-invasive alternatives in future are MRI guided focused high frequency ultrasound DBS, transcranial magnetic stimulation (TMS), transcranial electrical stimulation and Infrared LASER treatment. One evolving concept is combining TMS with electro Convulsive Therapy (ECT) for maintenance, especially for severe anxiety, pending controlled clinical trials (90).

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Commentary

Is Chronic Administration of Hydroxychloroquine Associated with Decreased All-Cause Mortality?

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Highlights of the Commentary:

- Acute or chronic administration of hydroxychloroquine has different effects in the body.
- Acute or chronic administration of hydroxychloroquine has no proven beneficial use in SARS-CoV-2 infection or COVID-19 disease, respectively.
- Available evidence suggests that chronic administration of hydroxy-chloroquine, as in the management of rheumatoid arthritis, may reduce cardiac- and all-cause mortality, apparently due to anti-inflammatory and immunomodulatory effects.
- The beneficial effects of chronic administration of hydroxychloroquine need to be further evaluated in randomized controlled studies.

Key Words: Hydroxychloroquine; Immunomodulation; Rheumatoid Arthritis; Lupus Erythematosus; SARS-CoV-2 Infection; COVID-19; All-cause Mortality

Introduction: COVID-19 pandemic has brought out hydroxychloroquine (HCQ), an old drug into the forefront of healthcare, albeit with conflicting reports. HCQ is in the World Health Organization's list of Essential Medicines (1). Its parent compound, chloroquine was discovered in 1934 by Hans Andersag. Since 1947 chloroquine has been in clinical practice, first as a drug for malaria, and subsequently approved for the treatment of rheumatoid arthritis and lupus erythematosus. FDA also approved chloroquine to treat extraintestinal amebiasis. Chloro-quine interacts with drugs like ampicillin, antacids, cimetidine, cyclosporine, and mefloquine. Chloroquine can cause acute hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked recessive genetic disorder affecting men. Chloroquine has a narrow therapeutic index. Hence, overdosing can be fatal. HCQ, the derivative of chloroquine is less toxic, and it largely replaced chloroquine in the United States and other countries. Both chloroquine and HCQ show comparable therapeutic properties.

HCQ has more than one mode of action, which apparently may find beneficial applications in the treat-ment of certain viral diseases. The earliest known action of chloroquine was its lysosomotropic property by which it can also inhibit autophagy (2). Through these properties, chloroquine acts as an anti-malarial drug by accumulating in endosomes and lysosomes of the parasite (2). This causes a rise in the internal pH in the endosomes. Low pH is essential for the function of these organelles, failing which the parasites cannot survive. Although the same lysosomotropic property of chloroquine has been alluded to its anti-viral activity (3, 4), there is not enough experi-mental evidence to prove this accounts for the anti-coronavirus activity of chloroquine or HCQ.

HCQ also appears to act as a zinc ionophore, allowing extracellular zinc to enter the cells (5). Zinc is a potent inhibitor of RNA-dependent RNA polymerase (RdRp), needed for the multiplication of RNA viruses, such as the coronaviruses (6). Although it has been shown that zinc ionophores inhibit RdRp activity in vitro, more studies must establish the preventive role of zinc against SARS-CoV-2 infection.

But the therapeutic effect of HCQ in rheumatoid arthritis (RA) and lupus erythematosus is due to its anti-inflammatory and immunomodulatory properties. These include inhibition of antigen processing and presentation, cytotoxic T lymphocytes, phospholipase A2 activity, nitric oxide formation in macrophages, matrix metalloproteinases activities, microRNA expression (7-10). HCQ inhibits production of interleukins, such as IL-1, IL-2, IL-6, IL-17 and IL-22, and interferons alpha and gamma (IFN-α and IFN-γ) and tumor necrosis factor-alpha (TNF-α) (11). These immunomodulatory effects of long-term HCQ therapy may benefit patients with viral diseases preventing the development of severe conditions such as cytokine storm, thus resulting in reduced mortality. Considering that suppression of inflammation and immunomodulation have beneficial effects in several chronic diseases, these properties of HCQ may have significant impact in overall mortality rate in patients with chronic diseases.

Clinical Study under Focus: Despite the above possibilities there have been very few studies on therapeutic benefits of HCQ in severe viral diseases, such as COVID-19 (12). In this context the recent publication by Gentry and associates in the *The Lancet Rheumatology* (13) sheds some light on the effect of chronic HCQ administration in high risk COVID-19 patients, namely Veterans. This retrospective cohort study evaluated whether patients with rheumatological conditions receiving chronic HCQ are at less risk of developing SARS-CoV-2 infection than those not receiving HCQ. Based on their findings, the authors concluded that HCQ was not associated with a preventable effect against SARS-CoV-2 infection in a large group of patients with rheumatological conditions. The infection rate with SARS-CoV-2 was low in both groups, 31 per 10,703 (0.3%) in HCQ group vs. 78 per 21,406 (0.4%) in control group. There were no significant differences between these two groups regarding hospital admission or intensive care requirement associated with SARS-CoV-2 infection. However, the mortality associated with SARS-CoV-2 infection was zero in the HCQ group vs. 7 per 78 (9%) in the control group (p = 0.19). Interestingly, the overall mortality was 88 (0.8%) in the HCQ group vs. 251 (1.2%) in the control group (p = 0.0031) (13). Another study showed that contrary to the general belief, there was no increased risk for adverse cardiovascular events or death with HCQ in Veterans with RA (14).

Discussion: Although, the number of SARS-CoV-2 infected patients in the above study by Gentry et al (13) was small to unequivocally conclude that chronic administration of HCQ reduced mortality due to COVID-19 in high-risk patients. i.e., Veterans, nevertheless, it is thought-provoking finding. Veterans have higher prevalence of diabetes mellitus, cardiovascular diseases (CVD), hypertension, and chronic kidney disease that predispose them for severe COVID-19 disease (15). In addition, the reported prevalence of obesity and/or overweight among Veterans is 40 to 73% (16), making them highly susceptible for mortality due to COVID-19 disease (17). These facts prompted us to consider the possibility of protective effect of chronic HCQ administration on overall mortality. A cursory search of literature provided additional support for such a possibility as presented in the following.

A population-based Danish cohort study examined whether chronic use of HCQ would affect the incidence rates of CVD, type-2 diabetes mellitus, cardiac- and all-cause mortality among RA patients (18). The study found a significant reduction in all-cause mortality and cardiovascular related death among HCQ users, with a hazard ratio of 0.83% (95% C, 0.71-0.97I) vs. 78% (95% CI, 0.61-0.99), respectively.

CVD is the leading cause of death in RA patients. In a retrospective RA cohort study conducted from January 2001 to October 2013, Sharma and associates (19) evaluated the association of HCQ with risk of diabetes, atherogenic lipid profile, and thrombotic activity with CVD in RA. The study excluded patients with CVD before RA diagnosis. The primary outcome was adjudicated incident of CVD defined as composite artery disease, stroke, transient ischemic attack, sudden cardiac death, and peripheral artery disease with arterial revascularization procedure. During the observation period, 102 CVD events occurred, 3 in HCQ users and 99 in nonusers. Thus, it appears that HCQ use was associated with marked reduction in the risk of incident CVD in RA patients, thereby warranting randomized control studies of HCQ use for primary prevention of CVD in RA or non-rheumatic high-risk patients (19).

Another study by Jorge and associates (20) determined the potential impact of HCQ use on the risk of mortality among patients with systemic lupus erythematosus (SLE) in general population. In this nested case-control study comprising an incident SLE cohort from the entire population of British Columbia, Canada, each deceased patient was matched with up to 3 living control subjects by age, sex and SLE disease duration. Conditional logistic regression was used to assess the risk of all-cause mortality associated with current or recent HCQ exposure compared with remote HCQ users. Data from this population study supported a substantial survival benefit associated with current HCQ use, and increased mortality among patients who had discontinued HCQ recently. The latter could be due to sick stopper effect or losing actual HCQ benefits.

Conclusion: There is no supporting evidence that chronic HCQ administration prevents infection with SARS-CoV-2 or saves life from severe COVID-19 disease. However, available evidence suggests that chronic administration of HCQ, such as in RA patients may decrease cardiac- and all-cause mortality. Further randomized controlled studies are needed to evaluate this potential health benefit of chronic HCQ administration.

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Synopses of Webinars and CME Lectures

This section contains non-peer reviewed synopses of Webinars and CME Lectures as submitted by the Speakers. They were only edited for clarity and language.

American Association of Nephrologists of Indian Origin

Synopsis of:

ANIO Special Virtual Zoom Webinar

June 7, 2021 8:30 PM EST/5:30 PM PST

Kidney Disease and Vascular Risk in South Asian Populations

The American Nephrologists of Indian Origin (ANIO) hosted a webinar on June 7, 2021 focusing on **Kidney Disease and Vascular Risk in South Asian Populations.** To better understand the burden of disease, risk factors, and strategies to help mitigate the risk, three accomplished physicians, Dr. Alka Kanaya, Dr. Nisha Bansal and Dr. Tazeen Jafar, shared their seminal works with the delegates.

Priya Deshpande, M.D.
ANIO Webinar Host
Assistant Professor, Division of Nephrology, Mount Sinai Hospital, NY
https://an-io.com/

This section contains non-peer reviewed synopsis of ANIO Webinar as submitted by the ANIO. The views expressed by the ANIO Speakers need not necessarily reflect those of AAPI.
A video recording of this webinar is available on the YouTube in the following link.
https://www.youtube.com/watch?v=IkEQAZ1Gd_U

Cardiometabolic Disease Among South Asians: Findings of the MASALA Study

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Highlights:

- South Asians have a higher metabolic risk than most other ethnic groups.
- Adipose tissue deposition in muscles, viscera, and pericardium may contribute to this increased risk.
- Chronic Kidney Disease (CKD) in the form of proteinuria is more prevalent in South Asian women in the United States as compared to those living in India.

Introduction: South Asians have the highest risk of heart disease as compared to any other ethnic groups (1). The reasons for this may be multifactorial: insulin resistance, hyperlipidemia, adiposity, lifestyle factors can contribute to developing type 2 diabetes mellitus (T2DM) and consequently atherosclerotic heart disease.

MASALA Study: Dr. Kanaya and her colleagues designed the Mediators of Atherosclerotic Disease in South Asians Living in America (MASALA) study which is the only prospective, longitudinal cohort study, to better understand the epidemiology of T2DM in South Asians in the US. The cohort consisted of 1,164 South Asians (over the age of 40; largely immigrants from South Asia to the US) who live in the greater San Francisco Bay Area and Chicago areas. At the time of recruitment into the study, the participants did not have existing cardiovascular disease and had not had interventions/surgeries on their heart or vasculature. The MASALA study was similar in design to the Multi-Ethnic Study of Atherosclerosis (MESA), to make valid comparisons to White Americans, African Americans, Hispanic Americans, and Chinese Americans.

- **Findings of the MASALA study:** The MASALA investigators have evaluated the behavioral characteristics, diet, prevalence of CKD, body composition and T2DM. Lifestyle and behavioral analysis showed that South Asian participants exercise significantly less than the MESA cohort participants. Dietary examination in the MASALA cohort showed that 33% followed a Western diet with animal protein, 33% followed a diet with fried snacks, sweets and high fat dairy, and 33% followed a diet of fruits, vegetables, legumes and nuts. The first two types of diets were associated with higher weight, waist circumference, hypertension and dyslipidemia.

- **CKD in the MASALA Study:** Investigators compared the CKD prevalence and epidemiology in the MASALA cohort to the Centers for Cardiometabolic Risk Reduction in South Asia (CARRS) cohort (2). The CARRS population were South Asians living in Chennai and Delhi, India and Karachi, Pakistan. They found that the prevalence of CKD in men was similar in the MASALA and CARRS cohorts, however women in the MASALA cohort had a higher prevalence of CKD due to more albuminuria. The MASALA cohort had better hypertension control and more usage of renin-angiotensin system inhibitors (2).

- **Body Composition and T2DM in MASALA:** The final part of the talk examined body composition and T2DM in the MASALA cohort. Dr. Kanaya highlighted the Yudkin-Yajnik paradox where for the same body mass index, there was increased adiposity in Dr. Yajnik (South Asian) versus Dr. Yudkin (European) cohorts (3). The South Asian body composition consists of hidden fat stores in the liver, muscle, pericardium and viscera. Metabolically, South Asians in the MASALA cohort were found to have higher levels of insulin resistance and poorer beta cell function, thus predisposing this population to diabetes. As compared with the MESA cohort, the MASALA cohort showed a prevalence of diabetes of 26.3%, which was higher than that in Whites, African Americans, Hispanic Americans and Chinese Americans (1).

Take Home Points: South Asians are at a high risk of T2DM and complications (CKD, cardiovascular disease) and this may be due to several factors such as lifestyle and behavioral, and body composition. More research is needed to understand how risk factor modification can help prevent end-organ dysfunction.

Disclosure: The speaker declares no competing interests.

Assessment of Kidney Function in South Asian Populations

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Highlights:

- Understanding the correct glomerular filtration rate (GFR) for a patient is essential for CKD treatment decisions, including medication initiation (SGLT-2 inhibitors), referral for vascular access placement and transplant referral.
- We rely on equations, mainly MDRD and CKD-EPI, to provide the estimated GFR (eGFR).
- CKD-EPI equation is currently the best option among available equations for estimating GFR in South Asian patients
- Other equations (the CKD-EPI Pakistan equation) as well as other kidney filtration markers may be promising alternatives to better estimate GFR in South Asians

Introduction: Accurately obtaining the GFR for a patient is essential in the treatment and management of Chronic Kidney Disease (CKD), and other comorbid conditions. Currently there is an extensive debate about using race in estimated GFR equations (Modification of Diet in Renal Disease, MDRD, and the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI). In the current format, race is denoted as "Black" and "non-Black" and adjustment for race results in the higher eGFRs for a given serum creatinine in Black adults as compared with non-Black adults. Removal of this adjustment will reclassify a third of Black adults into more severe CKD staging categories. The current race-based equations may be biased and delay transplant eligibility for Black patients. It is unclear how to approach eGFR in South Asians given the heterogeneity of the population and whether the "Black" or the "non-Black" equation should be used.

"Normal" GFR in South Asians: Based on a study done by Dr. Tazeen Jafar published in the American Journal of Kidney Diseases in 2015, the mean GFR based on inulin clearance in Pakistani men and women (530 subjects, age >40 years, without T2DM or hypertension) was 94.1 ± 28 mL/min/1.73 m^2 and declined by 0.79 ± 0.11 mL/min/1.73 m^2 (4). In comparison, the European GFR at age 20 years, was 125 mL/min/1.73 m^2 and declined by 1 mL/min/1.73 m^2 (2, 4).

Optimal eGFR Equation in South Asian People: The CKD EPI formula was better as compared with MDRD based on a multi-ethnic study done by Teo et al published in the American Journal of Kidney Diseases (AJKD) in 2011 (5). Jessani and Jafar compared the MDRD, CKD-EPI and a modified CKD-EPI formula for Pakistanis (CKD-EPI PK) and found that the CKD-EPI was better at accurately predicting GFR as compared with MDRD. The CKD-EPI PK equation improved the performance of the CKD-EPI equation in South Asians (4).

Alternatives to Creatinine-based eGFR Measurements: Cystatin C-GFR was evaluated in Pakistani patients as well and it was found that it underestimates eGFR. The CKD-EPI equation that takes both creatinine and cystatin C into account was not substantially better than CKD-EPI PK.

Take Home Points: The CKD-EPI formula is more accurate for estimating GFR for South Asian people. More research is needed to evaluate specific South Asian-developed equations and other markers for kidney filtration.

Disclosure: The speaker declares no competing interests.

Management of Hypertension and Cardiometabolic Risk Factors in South Asians

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Highlights:

- South Asian people are at risk of developing Chronic Kidney Disease (CKD) and cardiovascular disease (CVD).
- There is a need for systems approach in order to prevent them.
- Control of Blood Pressure and Risk Attenuation-Bangladesh, Pakistan and Sri Lanka (COBRA-BPS) is one of the first studies that demonstrated that a Community Health Workers (CHW)-led intervention is uniformly effective. cost-effective, scalable and affordable strategy for controlling blood pressure

Introduction: A systems approach is needed to influence global policy to target atherosclerotic disease in South Asians, particularly those who live in lower-middle income countries like Pakistan, India, Bangladesh and Nepal. South Asian people are at a higher risk of developing CKD and CVD not only because of individual characteristics (i.e. weight gain, insulin resistance, T2DM, increased inflammatory milieu) but also because of societal disparities (as poverty, access to health care, tobacco use and education level), and environmental exposures (nephrotoxic drugs and chemicals) (6). Metabolic changes such as hyperinsulinemia and dyslipidemia can be seen in South Asians at a younger age , and these children have higher blood pressure as compared with white children of similar age and body mass index. As a result, CKD and CVD manifest 5-10 years earlier in South Asians as compared with Europeans.

COBRA BPS Trial: Dr. Jafar particularly focused on systemic strategies to better control hypertension since significant gaps exist (e.g., less than half of patients have received the diagnosis of hypertension and less than a third are well controlled). The findings of this study were published in the New England Journal of Medicine in February 2020 (7. 8).

Design: Dr. Jafar spearheaded the COBRA BPS trial, a randomized control trial that was conducted in 30 rural communities in Bangladesh, Pakistan and Sri Lanka. The intervention was a "multicomponent" strategy in which trained Community Health Workers (CHWs) provided home based hypertension education. The CHWs were supported by trained general physicians in the public health sector (i.e. CHW identified patients with elevated blood pressure and they were then referred to clinic for hypertension treatment and management, and tracked by the CHWs using checklists).

Findings: As compared with usual care, this home-based concerted "multicomponent" effort resulted in a 9 mm Hg blood pressure reduction (as compared with 3.9 mm Hg decline in the usual care group over 2 years. Reduction in mean diastolic BP and BP control (<140/90 mmHg) was also better in the intervention group. The intervention increased adherence to antihypertensive medications and lipid-lowering medicines, and improved some aspects of self-reported health. Additionally, there was an indication of a reduction in deaths from cardiovascular disease in the intervention group. The annual per capita cost of intervention delivery was less than US $2 annually.

Conclusion: The multicomponent intervention in rural Bangladesh, Pakistan and Sri Lanka resulted in greater reductions in blood pressure. Also, this strategy was an affordable solution to help prevent deaths and disability because of hypertension.

Take Home Points: Improving outcomes in hypertension in lower-middle income countries using CHWs supported by trained general practitioners and public health agencies is an affordable, sustainable and realizable goal. This strategy can prevent increased morbidity and mortality associated with hypertension.

Disclosure: The speaker declares no competing interests.

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Link to a Recent Webinar Conducted by the ANIO

ANIO and the Kidney (Conversations from NY and India)

June 26, 2021

This was a conversation between American Nephrologists of Indian Origin (ANIO), and Indian Nephrologists for exchange of experiences and views regarding COVID-19 and its impacts (renal and non-Renal) in the immediate, intermediate, and long-term; how should we, as healthcare providers be developing our response and opportunities for research and collaboration.

https://youtu.be/0UPL0C6XKxQ

Synopsis of AAPI Webinar – June 14, 2021

A Special Tribute to COVID-19 Healthcare Heroes

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Objectives of the Presentation:

- Discuss Differences in epidemic compared to last year
- Discuss differences in clinical presentation compared to last year
- Discuss common treatment practices for COVID-19 and Clinical Impact
- What is SHARE INDIA doing to address the COVID-19 situation in India

Difference in Epidemic Compared to Last Year: As a clinician involved in the care of patients with COVID 19 illness since early 2020 the following are my observations: In 2021 compared to 2020, we see an enormous increase in number of patients and often entire families affected simultaneously with no one left as a caregiver. A larger proportion of infected individuals are progressing from milder to severe illness in a shorter time frame (Telescoping). Recovery is taking place over an exceptionally long time with persistent elevation of markers of inflammation (CRP) and frequent recurrence of symptomatic illness in people a few days after stopping anti-inflammatory medicines.

Differences in Clinical Presentation Compared to Last Year: Many individuals are presenting after one dose of vaccine and some soon after second dose of vaccine. Even post recovery, some individuals have chest syndrome (pleuritic, pericarditis pain), tachycardia, disabling fatigue with a few expiring due to sudden death (cause unknown). Explosive increase in demand for High-Resolution CT (HRCT). There is an explosive increase in demand for Remdesivir, and an epidemic of treatment with questionable regimens (doxycycline; ivermectin; high dose vitamin C, vitamin D, zinc, high dose steroids, antibacterial, proton pump inhibitors). There is collapse of public hospital systems, which are not consistently providing dexamethasone and anticoagulants to patients who require supplemental oxygen.

COVID-19 vs. Previous Coronavirus Outbreaks: COVID 19 is clearly different in both clinical manifestations and epidemic dynamics as compared to SARS and MERS in having a greater transmissibility despite lower case fatality rate. The number of infected (larger denominator) has a greater socio-economic impact. COVID 19 has a greater propensity to evolve into genetically heterogeneous populations best described as, viral quasispecies evolution (1). This explains the emergence of the Alpha, Beta, Gamma, Delta ….. variants we have been seeing and will continue to see.

India vs. United States: The difference between India and the United States in morbidity and mortality has been attributed to differences not only in the demographics of the population, but also social mores, and access to advanced medical care. Fortunately, most vaccines have efficacy (albeit somewhat lower than before) against the newer variants of interest. This has implications for how we address the pandemic in India and also how we plan for the eventuality of similar emerging pandemics.

Role and Work of SHARE India: SHARE INDIA (Society for Health Allied Research & Education India) was formed and registered in 1986 as a research society and recognized as Scientific and Industrial Research Organisation (SIRO), by Ministry of Science & Technology, Government of India. The vision of SHARE is to strive to create healthy population by innovation and increasing, imparting and applying knowledge. The objective is to provide comprehensive, effective, affordable health care to people and build capacity for innovation/research to address health care challenges of today and the future. In 2020 at SHARE INDIA, we developed a projection of the spread of infection in the Telangana State population using the SIR model (R0=3), According to our projection, an estimated number 11,910,208 individuals (36% of the population) of Telangana State would have COVID-19 infection, which we submitted for publication and pre-print

is available online (2). Our projections were perhaps overly optimistic and the R_0 of 3.0 was an underestimate. As of June 11, 2021, the actual epidemic numbers as reported by Johns Hopkins are clearly much greater than expected.

Using the logistic map equation **Xn+1= rXn(1- Xn)** and revised R_0, it is far more likely that the epidemic will be cyclical with the periodicity of the peaks and troughs yet to be determined, with an R_0 between 3 and ≈ 3.44949, from most initial conditions the population will approach permanent oscillations between two values. The implications of this concept are:

1. We probably will see the epidemic numbers decline in few weeks followed by an inevitable rise in cases within a few months of the decline. The only significant change in the dynamics of epidemic is possibly the ability to vaccinate over 75% of the population (including children) within the next 6 months. There are significant concerns about the safety of vaccines in children due to a more robust immune response in younger children. It is important to understand that in India, children (0-14 years) constitute ~ 28% of the population. We have seen that children easily acquire and transmit respiratory tract infections with mild illness, but serious illness when transmitted to adults. Both mycoplasma and chicken pox are classic examples. This has serious implications for schooling, in India, and relying on distance learning (internet) is not widely available.
2. We need to prepare to take care of the affected people in the community rather than in hospitals for 3 reasons:
   a) In India ~ 65% of the population is rural with negligible access to adequate medical care.
   b) We do not have enough capacity in public hospitals to handle the burden (private hospitals are not an option for the average citizen) even in urban areas.
   c) Concentrating large numbers of infected people in small areas (particularly poorly ventilated areas) increases the risk of transmission to other people particularly health care providers and increases the probability of emergence of yet newer variants (mutants) of the virus that may be more contagious and capable of causing more serious illness. Many decades ago, Paul Ewald suggested that all populations of living organisms always evolve strategies for perpetuation of the species regardless of consequences to the host (3).
3. We need to have a plan to address not only the acute illness caused by COVID-19 infection but also:
   a) Economic impact of illness on the patient and family
   b) Socio-economic impact of "Lockdown" etc.
   c) Long term complications of COVID-19: Lung damage, infections like tuberculosis, fungal infections ("Black Fungus")
   d) Long term complications of inappropriate treatment regimens of COVID-19 (overzealous use of high dose steroids, tocilizumab, remdesivir, Ivermectin, convalescent plasma)
   e) Long term disability caused by COVID-19 and consequent loss of ability to earn a livelihood.

SHARE INDIA has been supporting the response to the COVID-19 pandemic in India through multiple programs:

A) Continuity of care despite the disruptions caused by lockdowns for:
   1. HIV infected individuals on anti-retroviral therapy
   2. Individuals with MDR/XDR tuberculosis particularly in the slums of Dharavi
B) Capacity building in laboratory diagnosis for COVID-19
C) Infection Prevention and Control in Government Hospitals
D) Epidemic intelligence and response support for the Maha Kumbh (April 7 to May 15, 2021)

SHARE INDIA has proposed a decentralized comprehensive approach to the pandemic: **COCOM HAPPEN INDIA (Community Outreach Program to Reduce Risk of Hospitalization and Hypoxia)**

- Each Outreach Worker (ORW) should be armed with **Pancha Astra** (Five Instruments)
- Masks
- Hand sanitizer
- Oximeter
- Dexamethasone (no more than 8 mg daily)
- Rivaroxaban (10 mg daily)
- While doing battle in the field each ORW should be able to monitor the following **Pancha Guna (Five Characteristics)**
- Symptoms and signs suggestive of COVID-19
- Oxygen saturation at rest and with exertion (6 min walk) respiratory rate
- Body weight (BMI)
- Random blood glucose
- Blood pressure

- In addition, use **photovoice** to record:
- Personal perspective of illness
- Family perspective of illness
- Impact on daily life activities
- Impact on livelihood
- Any other symptoms consistent with PASC (Long Haul COVID)

Recorded Webinar Presentation: A recorded video of this webinar presentation can be accessed in the following link https://www.youtube.com/watch?v=rfG-eql_lfo&t=3s

Disclosure: The author is the head of Infectious Diseases and Public Health at SHARE India (www.shareindia.org), while being a Clinical Professor of Medicine and Surgery at the University of Illinois at Chicago, Illinois, USA.

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Synopsis of CME Lecture – 39th Annual AAPI Convention 2021

Reverse Epidemiology of Obesity Paradox: Fact or Fiction?

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Highlights: Obesity paradox (OP) refers to the observation that when acute cardiovascular (CV) decompensation occurs, obese patients may have a survival benefit. This runs counter to the epidemiology of obesity, which is known to lead to CV diseases (CVD) and other conditions. This synopsis:

- Defines reverse epidemiology of OP, and its proposed role in overall mortality in chronic diseases of heart, kidney, and lung, and in aging population.
- Delineates evidence for and against obesity paradox, and the importance of using different indices of body mass to assess risk in chronic diseases.
- Presents clinical picture and pathophysiology of emerging problem of lean diabetes in Asians and Africans.

Introduction: Obesity causes several diseases, such as type-2 diabetes mellitus (T2DM), hypertension, CVD, dyslipidemia, cancers, liver diseases, and reproductive disorders, among others. OP does not question the role of obesity in developing these diseases. OP deals with apparent beneficial effect of body fat against risk of mortality once people develop the diseases due to obesity. The term "reverse epidemiology" was first proposed by Dr. Kalantar-Zadeh in the journal Kidney International in 2003, and then in the Journal of American College of Cardiology in 2004. It contradicts prevailing medical concepts of prevention of atherosclerosis and CVD. OP, in its simplest form is defined as: *when acute cardiovascular decompensation occurs, obese patients may have a survival benefit*. The OP was first described in 1999 in overweight and obese people undergoing hemodialysis. Subsequently, it was found in those with heart failure, myocardial infarction, acute coronary syndrome, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and elderly people in nursing homes. Meta-analyses of several clinical studies support the existence of OP.

Critiques of Obesity Paradox: However, not everyone agrees about OP. Critiques argue: (i) body fat is helping patients to survive during periods of low nutrition; (ii) non-obese population includes patients who have lost weight because of more severe illness; (iii) obese people are being diagnosed earlier; (iv) body mass index (BMI) poorly represents body fat; (v) BMI cut-offs are not appropriate; and (vi) the observed OP is due to Collider Stratification Bias. While the first three points can be verified or eliminated in carefully controlled studies, the argument about BMI is counterintuitive, as the same BMI is used as benchmark in epidemiological studies which revealed that obesity leads to diseases. Collider for a certain pair of variables is a third variable influenced by both. A collider can introduce a spurious association between the cause and effect, and thus negatively affect the outcome, i.e., instead of obesity resulting in mortality, it may actually protect against mortality. In this respect, a collider differs from a confounder. However, experts have shown that collider bias alone cannot fully explain OP. Collider bias explains only a small discrepancy between the association and the causal effect observed; collider bias must be very strong to lead to an association that reverses the causal effect; and collider bias does not apply when population is unselected, and we know that OP is not selective.

Obesity Paradox vs. BMI Paradox: When BMI is used as the benchmark, there is J-shaped relation between it and mortality risk in subjects with no CVD, with the optimum BMI being between 20 to 25 Kg/m^2. But in subjects with established CVD, the relation between BMI and mortality risk becomes U-shaped with the optimum range of BMI shifting to 25 to 30 Kg/m^2. Interestingly, this phenomenon is not seen if waist circumference is the benchmark instead of BMI in the same populations. This observation prompted some experts to believe that what we see is BMI paradox, not OP. However, we knew that abdominal (visceral) adiposity leads to deleterious metabolic

disturbances, and subcutaneous fat accumulation has a benign effect on cardiometabolic risk. Based on this, several anthropometric indices that are independent of obesity paradox have been proposed. These can be used in routine clinical practice. Sophisticated imaging indices give even better analysis of distribution of fat depots in the body, but are not usable routinely.

Metabolically Healthy Obesity: Recently, the concept that metabolically healthy obese (MHO) phenotype can be promoted by exercise is gaining ground. Exercise promotes: (i) efficient fat storage and lipid formation; (ii) low extracellular matrix fibrosis; (iii) angiogenesis; (iv) adipocyte browning; and (v) low macrophage infiltration/ activation. These are associated with a distinctive "secretomic profile" of human adipose tissue, which is protective for the cardiovascular system. About 12% of obese individuals exhibit MHO, with one of these criteria: (i) no metabolic syndrome; (ii) no insulin resistance; (iii) high cardio-respiratory fitness (CRF); (iv) low visceral adipose tissue volume; and (v) low levels of systemic inflammatory mediators. MHO phenotype is characterized by low CVD risk. The MHO group have 30-50% lower risk for all-cause mortality and CVD compared to non-MHO subjects, and similar to that of metabolically healthy normal weight subjects.

CRF Influences Obesity Risk: Cardio-respiratory Fitness is a well-established independent predictor of CVD risk and all-cause mortality. Good CRF level reduces mortality risk by 44%. Being fit is more important than losing weight in terms of lowering CVD mortality risk. Unfit obese subjects have almost two-fold higher CVD risk compared to obese, but fit individuals. Obese fit subjects have lower CVD risk compared to normal weight, but unfit individuals (fat but fit).

Lean Diabetes: Also known as Atypical Diabetes, Malnutrition-related Diabetes, Tropical Diabetes and by other names, lean diabetes (LD) does not meet the classical ADA/WHO classification of T2DM, and it may be a hybrid of T1DM and T2DM. It is predominantly seen in men of Asian or African ancestry of poor socioeconomic status, with history of childhood malnutrition. It has an early age of onset, with absence of ketosis on withdrawal of insulin, and has higher total CV and non-CV mortality vs. obese diabetics. The LD also have increased risk of hypoglycemia and death. Asian LD have larger adipocytes with low levels of adiponectin and fatty acid breakdown, that age faster (cellular senescence). Thus, their adipocytes switch from "fat storage" to "fat spillage", and thus negatively affect CV system. They also have higher HbA1c, fasting and post-prandial blood glucose levels as compared to obese diabetics. Microvascular complications of diabetes (retinopathy), nephropathy and neuropathy are more common among LD male patients.

Thin-Obese Paradox Babies in India: Newborn babies in India are thin, but have higher fat mass relative to muscle mass (thin but obese). Genetic predisposition seemingly influences body composition and contributes to the Indian thin-obese paradox. It may originate in utero, and foster the development of diabetes in adulthood. It can be reversed by improving maternal nutrition.

Conclusion: Adiposity is not necessarily unhealthy, but it depends on regional distribution, the type of fat expansion, and adaptation to excess caloric intake. Metabolically benign adipose tissue exists, which can explain OP. The role of CRF in influencing OP is becoming obvious by allowing excess adiposity without causing adipocyte dysfunction. Future research on obesity should promote healthy fat storage, prevent adipocyte dysfunction, and develop novel molecular or imaging technologies for correct phenotyping of patients to capture properly the trajectories of mortality in a number of disease conditions. LD is emerging as a distinctive subtype of T2DM among men of Asian or African descent. Obviously, more clinical data with evaluation of current therapeutic methods are needed in to manage LD.

Take Home Message: Although it may appear to be an artifact, there is substantial evidence for OP. More controlled clinical studies are needed to understand the OP phenomenon and how it affects mortality in chronic diseases. The clinical characteristics, pathophysiology and mortality rate of LD pose new challenges for practicing physicians.

Disclosure: Author is an inventor on patents to prevent or treat diet-induced obesity, and is a Co-Founder, President, Chief Executive Officer and Chief Scientific Officer of ePurines, Inc., a drug development startup focused on purinergic signaling based therapies for obesity, metabolic syndrome, and kidney and liver diseases. Author declares this synopsis has been prepared with no industry or commercial support, but in the capacity of Adjunct Faculty at the University of Utah Health.

Synopsis of CME Lecture – 39th Annual AAPI Convention 2021

An Update on Guidelines for Cancer Screening

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Highlights:

- The top 5 organs of cancer related deaths are: 1) lung 2) colorectal 3) pancreas 4) breast 5) prostate. Lung cancer causes more deaths than colorectal, pancreatic and breast cancers combined.
- The United States Preventative Services Task Force (USPSTF) has published new recommendations for lung and colon cancer screening.
- Due to the pandemic, screening rates for all cancers suffered a dramatic decline.

Introduction: Cancer is the second most common cause of death in the United States, the first being heart diseases. Over 600,000 people were estimated dead from cancer in 2020 (and over 650,000 from heart disease), while approximately 345,000 were estimated dead from COVID-19. The top 5 organs of cancer related deaths are: 1) lung 2) colorectal 3) pancreas 4) breast 5) prostate. These five sites account for over half the number of cancer deaths. In fact, lung cancer causes more deaths than colorectal, pancreatic and breast cancers combined.

Lung Cancer Screening: Lung cancer is the number one cause of cancer death in both men and women. Lung cancer screening is a low dose, low resolution non-contrasted CT chest which should be done annually. The USPSTF has recently published new recommendations and the Centers for Medicare and Medicaid Services (CMS) is reviewing the update, with expected coverage expansion decision by mid-November 2021. Less than 10% of eligible patients are getting screened, even before the pandemic. Unfortunately, there is a large deficit in awareness due to stigma or fear associated with lung cancer.

Screening Criteria:

- 55 to 77 years old (up to 80 years, if commercial insurance)
    - **USPSTF update: 50-80 years**
- 30 pack-year smoking history
    - **USPSTF update: 20 pack year history**
- Still smoking or have quit smoking within the last 15 years
- Asymptomatic
- No Chest CT in the last year

Colorectal Cancer Screening: Colorectal cancer is the second most common cause of cancer deaths overall. Various modalities can be used for screening. A positive finding with a stool test would require follow up colonoscopy. USPSTF update expanded guidelines for eligibility from age 50 to 75 to **45 to 75.** USPSTF recommends selective screening in patients over 75 years old.

Screening Options:

- High-sensitivity guaiac fecal occult blood test (HSgFOBT) or fecal immunochemical test (FIT) every year.
- Stool DNA-FIT every 1 to 3 years
- Computed Tomography Colonography every 5 years
- Flexible Sigmoidoscopy every 5 years
- Flexible Sigmoidoscopy every 10 years + annual FIT
- Colonoscopy screening every 10 years

Breast Cancer Screening: Breast cancer is the most common cancer. There are various recommendations regarding age of onset and frequency. Some experts recommend screening starting at age 45, but most favor starting at age 55. Screening intervals vary from annual to once in every 2 years, but most favor the latter. Screening below age 45 and above age 75 should be an individual decision based on family history and life expectancy. Clinical Breast Exam is no longer recommended by most guidelines.

Prostate Cancer Screening: Prostrate cancer is the second most common cause of cancer death in men. Screening may include (but doesn't require) a digital rectal exam besides checking a serum prostate specific antigen (PSA) level. Patients should be offered informed decision at age 50 if they have average risk, or age 45 if at high risk, or age 40 if very high risk. African American descent and those with first degree relative diagnosed younger than age 65 are considered at high risk. Patients with more than one first degree relative who had prostate cancer at an early age are considered at very high risk.

Impact of Pandemic: There was a dramatic decrease in screening rates, as high 90%, during the pandemic. This impacted all cancer screening, estimating a deficit of over 9 million screenings. This translated to decreased biopsies, and ultimately fewer resections. Cancers that were diagnosed have typically been more advanced than the pre-pandemic levels. Though screening rates have increased since the nadir, levels never increased enough to compensate for the significant deficit. Estimates expect over 60,000 years of life lost (YLL) due to these delays.

Tips for Screening during Pandemic:

- Use mobile units and multiple option "1 stop shops" when feasible. For, example mobile mammography unit with ability for blood draws, dissemination of stool kits and administration of vaccines.
- Pair screening and vaccination events.
- Encourage increased non-invasive screening, for example, stool testing for colorectal screening, when possible.
- Enact proactive outreach to patients due for screening.
- Enhance social media communication to patients about risks of cancer and safety of screening procedures.
- Utilize telemedicine for Initial assessment and results and then follow-up if appropriate.
- Employ universal masking precautions (patient, clinician, and staff) as necessary.
- Practice social distancing precautions when possible
- Screen at sites separated from those with inpatient COVID-19 units (Outpatient Imaging Centers, mobile, etc,) when available.

Conclusion: Cancer is the second most common cause of death overall. Lung Cancer is the top cancer killer, regardless of gender. Yet, lung cancer screening rates were low even before the pandemic. Screening for all cancers dramatically declined during the pandemic, ultimately leading to a substantial increase in projected cancer deaths. Given this significant mortality, early detection and prevention needs to be reprioritized. Tobacco cessation should have more emphasis and patients with known risks should be screened regularly to reduce cancer mortality.

Take Home Message: Early screening for cancers saves lives. The updated guidelines provide several options for early screening depending on patient factors and available facilities in hospitals or clinics. Physicians should be proactive to reduce cancer related mortality.

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Synopsis of CME Lecture -39th Annual AAPI Convention 2021

Current Status of COVID-19 Vaccines

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Highlights: Vaccine development during the global coronavirus disease 19 (COVID19) pandemic has significantly changed the trajectory of the disease but has also raised numerous concerns pertaining to the various platforms due to the expedited process. This synopsis covers:

- Various coronavirus platforms, reviews the existing efficacy data, and explores vaccine effectiveness in special population.
- Explores more common and rare adverse effects attributed to these platforms,
- Discusses the current variants in circulation and existing data on vaccine effectives towards these variants.

Introduction: Vaccine development during the coronavirus pandemic has been achieved in a record-breaking time. A typical vaccine development process takes years to go through the various pre-clinical, clinical, and manufacturing stages prior to authorization and approval. Due to the accelerated vaccine timeline during the coronavirus pandemic, authorization for first COVID-19 vaccine was achieved in less than eight months after initiating trails. This was made possible as the newer mRNA platforms were already established and studied for prior coronaviruses such as the MERS, and some of the vaccine development stages were running in parallel.

Vaccine Platforms: There are three major coronavirus vaccine platforms:

Subunit Vaccines, which contain specific isolated antigen from the virus that sensitizes our immune system so it can mount appropriate immunological response to future exposures.

Viral Vector Vaccines, which contain a different virus coating serving as a vector to transport the genetic material (DNA) of the current virus. DNA is translated into protein (antigen) triggering the immune response.

mRNA Vaccines have viral mRNA enclosed in a lipid nanoparticle. Once injected, nanoparticles enter the cytoplasm releasing mRNA which is then translated into viral protein serving as antigen for the immune system (spike protein in case of COVID-19 vaccine).

Vaccines under Emergency Use Authorization (EUA) in the United States:

Pfizer BioNTech: administered to anyone above age 12; two doses given 21 days apart; fully vaccinated 2 weeks after the 2nd dose; 91.3% overall efficacy against COVID-19; 95% efficacy against severe disease caused by Alpha/Beta variants.

Moderna: administered to anyone over the age of 18; two doses given 4 weeks apart; fully vaccinated 2 weeks after the 2nd dose; 94.1% protection to prevent symptomatic SARS-CoV-2 infection, but the efficacy rate drops to 86.4% for people ages 65 and older.

Johnson & Johnson: Administered to anyone above the age of 18 as single-dose vaccine. One is fully vaccinated 2 weeks after receiving the dose. It is 74.4% effective for prevention of mild to moderate disease and 78% effective for preventing severe disease.

AstraZeneca, an adenovirus vector vaccine, and **Novavax**, a protein sub-unit vaccine are still under clinical trials in the United States.

Special Category of Populations: Special category of populations, such as pregnant women, children, and immunocompromised were excluded from the earlier clinical trials. Studies on such populations are ongoing.

Pregnancy: Currently, there are limited data regarding COVID-19 vaccination in pregnancy. No safety concerns were found in animal studies with Pfizer, Moderna, or J&J vaccines administered before or during pregnancy. Early data from safety monitoring systems is reassuring. In a recently published study from Israel in the *Journal of the American Medical Association*, Goldshtein et al reported findings of an observational/retrospective study looking at infection rates in 15,060 pregnant women, half of whom

were vaccinated with the Pfizer vaccine, and other half were not vaccinated (1). The authors found that infection rate was significantly lower in the vaccinated group when compared to the non-vaccinated group. There were no major vaccine associated adverse events reported even in pregnant patients who proceeded to term. This study was limited by its observational design and further controlled trials are warranted. As per current recommendations of Centers for Disease Control and Prevention (CDC), pregnant or lactating women are eligible for any of the currently authorized COVID-19 vaccines (2-4).

Pediatric Age Group: Vaccination studies in children are ongoing, but CDC recommends vaccinating children ages 12 years or older as mentioned above.

Immunocompromised Patients: CDC recommends that any of the currently authorized COVID-19 vaccines can be administered to immunocompromised patients including those who are on immunosuppressive medications. Initial studies in solid organ transplant recipients found that only 17% of the individuals produced "sufficient antibodies" after one dose of the two-dose mRNA regimen. Factors associated with higher antibody detection included younger participants, those with liver transplant, transplant duration >12 years, those who were not receiving anti–metabolite maintenance immunosuppression (antimeatbolite suppression includes mycophenolate, mycophenolic acid and azathioprine), and those who received the Moderna vaccine. In a follow up study, only 54% of the 658 participants had a detectable antibody response at a median day of 29 after the second dose, This study highlighted that 46% of participants had no measurable antibody response after both doses and 39% of participants who had no response after the first dose, but a subsequent antibody response after the second dose had antibody levels which were relatively lower than those seen in immunocompetent patients. As a result, clinical trials are needed to assess the effectiveness of a third dose of vaccine in this patient population.

Adverse Events: The most commonly reported adverse events are similar amongst the various COVID-19 vaccines and include fatigue, myalgia, headache, fevers, chills, nausea, pain, redness, and swelling at the site of injection. However, there are rare severe adverse events reported which are specific to vaccine platform.

Thrombotic Thrombocytopenia related to the adenovirus vector vaccines: this was initially reported in association with the AstraZeneca vaccine and presents with acute atypical thrombosis, primarily involving the cerebral veins with concurrent thrombocytopenia. It is seen in women of childbearing age, about 6 to 24 days after receiving the AstraZeneca vaccine. A novel underlying mechanism of anti-PF4 antibodies unrelated to the use of heparin was identified in these patients which behaved similar to HIT (heparin-induced thrombocytopenia). Avoidance of platelet transfusions is critical in these cases, as this can cause further antibody mediated platelet activation, coagulopathy, and further thrombosis. Although evidence does not yet suggest that using heparin will exacerbate this condition, current recommendations are to use non-heparin anti-coagulants. Initial control of disease can be achieved with intravenous immunoglobulins (IVIG) and plasma exchange.

Myocarditis and Pericarditis after mRNA Vaccines: More than a thousand cases of myocarditis and pericarditis have been reported to the Vaccine Adverse Event Reporting System (VAERS) after receiving the mRNA COVID-19 vaccine. These cases have occurred mostly in male adolescents and young adults ages 16 years or above. Incidence is higher after receiving the second dose rather than the first dose of mRNA based COVID-19 vaccines.

Guillian-Barré Syndrome (GBS): Recently, FDA issued a warning for J&J vaccine suggesting an increased risk of GBS. One hundred cases of GBS have been identified out of 12.8 million people who have been vaccinated. Further investigation is underway.

As these vaccines have been rolled out to the general population, and after-market data are crucial to identify rarer and more serious adverse events related to the COVID-19 vaccines.

Variants in Circulation: Until recently (as of June 19, 2021), the B.1.1.7 or Alpha lineage of the virus which was first spotted in the UK, was still the dominant variant in the United States representing ~47.8% of the cases. As of July 16th, 2021, the contagious Delta variant has become the dominant variant in circulation in the United States. Unvaccinated people are most at risk and therefore, regions with low vaccination rates may need to bring back local mask mandates. Recent studies provide varying data on mRNA vaccination effectiveness for the Delta variant (B.1.617.2). One concerning study from Israel suggested that the effectiveness of mRNA vaccines was reduced by 30%. Another "Delta Plus" variant (B.1.617.2.1 or AY.1) is in circulation in India.

Take Home Message: As the number of fully vaccinated individuals approach 50%, there is some sense of control

over the COVID-19 pandemic in the United States. This was largely possible due to the expedited development of these COVID-19 vaccination platforms. Vaccine hesitancy continues to push back the efforts to achieve herd immunity as the new contagious variants circulate faster raising concerns about the current relaxation of mandates. As most of the states have relaxed mask and social distancing mandates, the current data show significant rise in new COVID=19 cases throughout the United States.

Disclosure: Author declares no competing interests.

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- Hippocrates