




COVID-19 vaccines and their underbelly: Are we going the right way?

Bhabani Sankar Satapathy¹ | Gurudutta Pattnaik² | Rudra Narayan Sahoo¹ |
Sovan Pattanaik¹ | Ashish K. Sarangi³ | Venkataramana Kandi⁴  |
Snehasish Mishra⁵ | Ali A. Rabaan^{6,7,8} | Aroop Mohanty⁹ | Ranjit Sah^{10,11}  |
Ranjan K. Mohapatra¹² 

¹School of Pharmaceutical Sciences, Siksha O Anusandhan Deemed to be University, Bhubaneswar, Odisha, India

²School of Pharmaceutical Sciences, Centurion University of Technology and Management, Alluri Nagar, Odisha, India

³Department of Chemistry, Centurion University of Technology and Management, Alluri Nagar, Odisha, India

⁴Department of Microbiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India

⁵School of Biotechnology, Campus-11, KIIT Deemed-to-be-University, Bhubaneswar, Odisha, India

⁶Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia

⁷College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

⁸Department of Public Health and Nutrition, The University of Haripur, Haripur, Pakistan

⁹Department of Clinical Microbiology, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India

¹⁰Department of Microbiology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

¹¹Department of Microbiology, Dr. D.Y Patil Medical College, Hospital and Research Center, Dr. D.Y. Patil Vidyapeeth, Pune, India

¹²Department of Chemistry, Government College of Engineering, Keonjhar, Odisha, India

Correspondence

Ranjit Sah, Institute of Medicine, Kathmandu, Nepal.

Email: ranjitsah57@gmail.com

Ranjan K. Mohapatra, Government College of Engineering, Keonjhar 758 002, Odisha, India.
Email: ranjank_mohapatra@yahoo.com

Abstract

Background: Historically, a critical aetiological agent of health concern stays till eternity after its discovery, so shall it be with the COVID-19 outbreak. It has transformed human life to a 'new normal' with huge tolls on the social, psychological, intellectual and financial spheres.

Aim: This perspective aimed to collate numerous reported COVID-19 vaccine-associated adverse events and the predisposing factors. It focussed on the efficacy of mix-n-match (cocktail) vaccines to effectively counter COVID-19 infection to facilitate future research and possible interventions.

Material and Methods: Databases like Scopus, Pubmed and the Web-of-science were searched for published literature on 'adverse events associated with COVID-19 vaccine'. The reports and updates from health agencies like the WHO and CDC were also considered for the purpose. The details with respect to the adverse events associated with COVID-19 vaccination and the predisposing factors were compiled to obtain insights and suggest possible future directions in vaccine research.

Results: India stood strong to manage its health resources in time and turned into a dominant global vaccine supplier at a time when healthcare infrastructure of many countries was still significantly challenged. Developing indigenous vaccines and the vaccination drive in India were its major achievements during the second and the subsequent COVID-19 waves. The fully indigenous Covaxin vaccine, primarily as an emergency intervention, was successfully rapidly launched. Similar such vaccines for emergency use were developed elsewhere as well. However, all of these reached the marketplace with a 'emergency use only' tag, without formal clinical trials and other associated formalities to validate and verify them as these would require much longer incubation time before they are available for human use.

Discussion: Many adverse events associated with either the first or the second/booster vaccination doses were reported. Evidently, these associated adverse events were considered as 'usually rare' or were often underreported. Without the additional financial or ethical burden on the vaccine companies, fortunately, the Phase IV (human) clinical trials of their manufactured vaccines are occurring by default as the human population receives these under the tag 'emergency use'. Thus, focused and collaborative strategies to unveil the molecular mechanisms in vaccine-related adverse events in a time-bound manner are suggested.

Conclusion: Reliable data particularly on the safety of children is lacking as majority of the current over-the-counter COVID-19 vaccines were for emergency use. Many of these were still in their Phase III and Phase IV trials. The need for a mutant-proof, next-gen COVID-19 vaccine in the face of vaccine-associated adverse events is opined.

KEYWORDS

COVID-19 pandemic, COVID-19 vaccine, efficacy and safety, vaccine-associated adverse events

1 | INTRODUCTION

COVID-19 outbreak has had a huge toll on social, psychological, intellectual and financial spheres of life, horrifying all to a "new normal." Emerging from Wuhan city China, the virus has affected millions around the world, wave after wave.^{1,2} During the cruel consecutive waves during 2020–22, nations across economic-strata were almost standstill for months to years. COVID-19 demonstrated its epidemicity in few weeks after its emergence, grappling almost half of the global population. As countries including India still struggle to cope with the post-COVID scenario, global economy is in doldrums.^{3,4} Being the second largest populated country with thickly populated cities, the Indian healthcare infrastructure, public health awareness, government funding and the socioeconomy was significantly challenged.⁵ The pandemic also hugely contributed to depression, anxiety, domestic abuse in the society leading to an increased suicidal tendency.⁶ Unlike many developing nations, India indeed emerged a true warrior fighting the third COVID-19 wave valiantly, and the world witnessed and appreciated India's strong

strategic planning and mass vaccination program (<https://www.mohfw.gov.in/>). Developing indigenous vaccines and managing the vaccination drive efficiently were the major successes during the second and subsequent COVID-19 waves here. India well-managed its health resources in time and became an influential donor of COVID-19 vaccines to the deprived economies. Developed nations too depended for drugs like Paracetamol and Remdesivir particularly during the first wave, to which India responded generously in line with its basic cultural ethos, "*Vasudhaiva kutumbakam*" and "*Sarve bhabantu sukhinah*"; salutes for that.

The availability of COVID-19 vaccines within the crucial phase played the trick in altering the worrisome global scenario downside up. India showed relentless concerted efforts of healthcare professionals, biotechnologists and formulation scientists. It was indeed a very successful and strong collaboration of leading pharmaceutical biggies with the government-funded research laboratories that led to a tangible outcome, a developed vaccine. Covaxin, a fully indigenous vaccine primarily to administer as an emergency intervention (the human clinical trial is awaited), was successfully developed in a short

time period. Emergency use' vaccines Moderna of Pfizer-BioNTech, Covishield of Oxford-AstraZeneca, Sputnik V of Gamaleya, Verocell of Sinopharm, CoronaVac of Sinovac and Covaxin of Bharat Biotech were developed to counter COVID-19, and administrated worldwide.⁷⁻⁹ Although the likely adverse events associated with these conditionally-approved COVID-19 vaccines are reported after they were gradually observed with time, they remain as the best weapons against the pandemic.¹⁰ This article reports the challenges in vaccine development, vaccine efficacy, vaccine-associated adversities and the need of next-gen vaccines to counter all the COVID-19 variants.

2 | VACCINE-ASSOCIATED ADVERSITIES

The SAGE (strategic advisory group of experts) formed and coordinated by World Health Organization (WHO) analyses the immunization and clinical trial results worldwide across various zones with the evidence of the impact, prognosis factors and probable pathophysiology of the disease. It would recommend whether and how the vaccines are used considering the regulatory guidelines, based on its internal assessment.¹¹ GACVS (global advisory committee on vaccine safety), another wing of WHO, monitors the effects of approved vaccines on the target population. It is a leading body that identifies and collates adverse events following vaccination. SAGE and GACVS consist of independent group of experts across science disciplines to look into the scientific merits, technicalities of vaccination and authoritative delivery, and frequently recommend scientific advisories to the WHO on safe use. Although adverse events associated with approved vaccines have been reported quite likely the expert panels subsidize regulatory protocols in view global emergencies like COVID-19.^{9,12}

In most cases, vaccine-associated adverse events are not reported through proper channel, go unaccounted/under-reported, or are recognized as "usually rare" cases if noticed. Such cases lose focus for further scientific analyses by design. Reports of cardiac complications like myocarditis and pericarditis, mostly after the second dose, persisted with messenger RNA (mRNA) COVID-19 vaccines. Available data correlate mRNA vaccination with the symptoms.¹³ Following the second dose of Pfizer-BioNTech vaccine, 40.6 young males of 12–30 age group per million reported myocarditis.¹⁴ Cardiac arrhythmias along with myocarditis and pericarditis after mRNA vaccination were reported in the United States, the EU, and Israel.¹⁵⁻¹⁷ Although a plausible relationship between myocarditis and mRNA vaccine is claimed, it lacks validation.

Serious cases of blood clot accompanied by low platelet counts after the second dose of AstraZeneca and J&J COVID vaccines are reported.^{18,19} Referred as TTS (thrombosis with thrombocytopenia syndrome), such complications were observed in the Europe and the United States within 3–30 days after vaccination.²⁰ The United Kingdom, Germany, and Norway reported cerebral venous thrombosis and thrombocytopenia during Phase III clinical trial of AstraZeneca vaccine.²¹ There are reports of thrombocytopenia with low platelet

counts with Vaxzevria and Covishield vaccination.²² Postural orthostatic tachycardia syndrome has been found to be mRNA vaccine associated. Bell's palsy syndrome, Guillian Barre syndrome, vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) causing life-threatening adverse reactions were observed in few cases. The GACVS subcommittee updated its statement on AstraZeneca vaccine associated blood coagulation events.²³ Many vaccines were approved to be marketed in the United States and elsewhere. Only a few, predominantly, Pfizer-BioNTech, Moderna, Covishield, and J&J/Janssen dominated the US market. The CDC suggested restricted emergency use of J&J/Janssen COVID-19 vaccine owing to safety concerns. The occurrence of adverse effects was about 4–6 people in every million vaccinated, although data on symptoms show that the impact varied between age group, sex, and geographical location. However, a due diligent collection of clinical data is in question. While available data suggest an increased risk in younger adults, further research to identify the exact mechanism behind TTS and the role of COVID vaccines across various age groups is underway. Long-term data analyses to decipher COVID-19 vaccine-related myocarditis and pericarditis and investigating into specific biological mechanisms behind such acute cardiac complications following vaccination need to be prioritized.¹⁷

The Indian experience of Sputnik V vaccination reports swelling of throat, difficulty in breathing, increase in blood pressure and convulsions as pathological conditions.²⁴ Common side-effects of Covishield and Covaxin vaccination in India were swelling at injection site, abdominal pain, fever, irritability, headache, etc.,²⁵ although Indian reports on adverse effects of COVID-vaccines are sketchy. The side-effects associated with Covaxin and Covishield vaccines seem much similar differing in their manifestation and severity. The data presented during a meeting of the National AEFI Committee of the Ministry of Health and Family Welfare, Government of India showed a total of 617 Covaxin, Covishield and Sputnik V vaccination associated seriously adverse events, after the first dose. A total of 180 adverse events ultimately resulted in death following the second dosage.²⁶ A survey noticed that more than 50% vaccinated individuals experienced musculoskeletal side-effects. Out of a total 1729 vaccinated, 80.7% were Covishield vaccinated while 17.8% Covaxin. Among them, 38.9% had received only a single dose while 61.1% received both the doses.²⁷ A series of adverse events at an average of 136 cases in every 1000 vaccinated within a week of the first Covishield dose was reported in a survey in rural health training centers around Faridabad, Haryana. Out of all vaccinated, 97 recipients reported serious issues of which about 76.3% reported it in 24 h post the vaccination.²⁸ Another survey reported 413 (74.82%) adverse cases out of 1112,²⁹ the adverse experiences being majorly in 18–40 years age group. The majority (913; 82.10%) received Covishield among the 1112 vaccinated cases surveyed, while 199 (17.90%) received Covaxin. Among the observed recipients, "break-through" infections were observed in 7.91% cases, where males had a higher (57.96%) risk than the females (42.04%).²⁹ Vaccine-associated adverse events and the predisposing factors are presented in Table 1.³⁰⁻³²

TABLE 1 The vaccine associated adverse events and the predisposing factors.

Vaccine type	Vaccine name	Mild adverse event	Severe adverse event	Predisposing factor
mRNA vaccine	Pfizer-BioNTech (BNT162b2)	Sore throat, headache, fatigue, myalgia, joint pain, nausea, muscle spasm, chills, fever, sweating, dizziness, flushing, feelings of relief, localized swelling, itching, tingling, brain fogging, anorexia, sleep issues, diarrhoea, nasal stuffiness, and palpitations ³⁰⁻³²	Injection site pruritus for more than a week and pain (excluding headache, muscle and joint pain), severe persistent lymphadenopathy, Bell's palsy ³⁰⁻³²	Previous history of allergy to food, drugs or vaccines like the ARV and influenza vaccines ³⁰⁻³²
	Moderna (mRNA-1273)	Similar reactions as above, and predominance of fatigue ³⁰⁻³²	Non-anaphylaxis allergic reactions, anaphylaxis reactions ³⁰⁻³²	Second dose of vaccine ³⁰⁻³²
Viral vector vaccine	Oxford-AstraZeneca/Covishield (ChAdOx1 nCoV-19)	Injection site pain, feverish feeling, muscle ache and headache ³⁰⁻³²	abdominal cramps, postural drop in blood pressure, loose stool, syncopal attack; fever above 40°C ³⁰⁻³²	People below 55 years of age, first dose ³⁰⁻³²
	Janssen (Ad26.COV2-S [Recombinant])	Headache, injection site pain, fatigue, muscle ache, nausea ³⁰⁻³²	Tachycardia-associated anxiety, chest pain, hyperventilation, dyspnea, paresthesia, light-headedness, hypotension, headache, pallor, syncope, clotting disorder ³⁰⁻³²	Not reported
	Gamaleya-Sputnik V	General discomfort, headache, chills, fever, arthralgia, myalgia, asthenia, and local reactions like injection-site tenderness, hyperaemia and swelling ³⁰⁻³²	Not reported	People below 55 years of age ³⁰⁻³²
Inactivated vaccine	Sinopharm-Verocell	Injection site pain, while systemic AEFI are headache, fatigue, myalgia, fever, arthralgia, dyspnea, cough, nausea, diarrhea and pruritus ³⁰⁻³²	Not reported	After first dose ³⁰⁻³²
	Sinovac-CoronaVac	Injection site pain, headache, fatigue, myalgia, arthralgia ³⁰⁻³²	Serious allergic reaction with urticaria 48 h after the first dose ³⁰⁻³²	Predominant in females ³⁰⁻³²
	Covaxin	Injection site pain, fever, headache, fatigue, nausea ³⁰⁻³²	Not reported	First dose ³⁰⁻³²

In every million vaccinated, 457 deaths were reported from Covishield and 20 from Covaxin. Both Covaxin and Covishield vaccines manifested reacted adversely at about 0.01% rate. As the data seem insignificant, it seems many cases might have gone unnoticed/unregistered. Among Indian states, Maharashtra registered the highest (4521) vaccination-associated adverse events followed by Kerala (4074), Karnataka (2650) and West Bengal (1456).³³ Many casualties were classified as coincidental, unclassifiable or undefined in case reports published by governments that failed to determine the root cause, exposing the underbelly of healthcare systems. Such reports may need serious investigation to decipher the cause-effect relationship of vaccination adverse effects.

3 | CHALLENGES IN VACCINE DEVELOPMENT

The efforts do not end as COVID-19 is still round the corner with new variants that exhibit unexplored mutation phases with new treatment/prevention challenges. With the passage of time, emerging forms like Omicron and its variants are threatening the world wherein the potency of the existing vaccines is questioned. Omicron variant, with rapid mutation rate, encodes more than 37 amino acid substitutes in the spike protein, which indeed challenges vaccine development strategies.³⁴ Many questions on the Phase III clinical trials during the early approval of vaccines including the rationality of subject selection, bypassing technical regulatory, dearth of post-marketing surveillance reports, etc. are unanswered. Historically, an etiological agent of serious health concern stays ever after its discovery, and in light of this fact the human civilization is at crossroads to adopt living with COVID-19 following the COVID-appropriate norms, the "new normal."

4 | BIVALENT COVID-19 BOOSTER AND COCKTAIL VACCINES

The available bivalent COVID-19 vaccines include the original virus strain and the Omicron components. Developed by Pfizer and Moderna, the two leading vaccine manufacturers, these are preferred as boosters allegedly to protect against Omicron. In the face of rapid alteration in viral genetic makeup, it is really difficult to assess whether these boosters would really be effective against the infection.³⁵ To counter COVID-19 infection effectively, vaccine mix-n-match (vaccine cocktail) gained popularity. SAGE too has advocated in favor of a third dose of Pfizer-AstraZeneca (heterogeneous) vaccine cocktail in case of unavailability of original vaccine. However, the potency, safety, cell-specific interaction or the long-term effect/risks of such cocktail on larger population need validation.³⁵

The GACVS subcommittee recommended that all countries should monitor the safety of the approved COVID-19 vaccines, and could promote reporting of the suspected adverse events. Such

recommendations seemingly are not taken seriously by most government regulatory agencies. While data on the Phase IV clinical trials of Moderna, Vaxzevria and Covishield vaccines are available, post-market surveillance reports on other vaccines, especially from the low income countries, are scanty. In the face of such apprehensions, few queries that need to be urgently addressed are, like, whether the vaccine mix-n-match strategy technically sound, whether the clinical safety of the vaccine-cocktail evaluated, whether the vaccines are safe for women with periods, lactation or pregnancy, whether the vaccines are safe for children and whether ample of multi-centric Phase III clinical data available to support it, and what is the specific roadmap for people on chronic medication or are moderately immunocompromised.

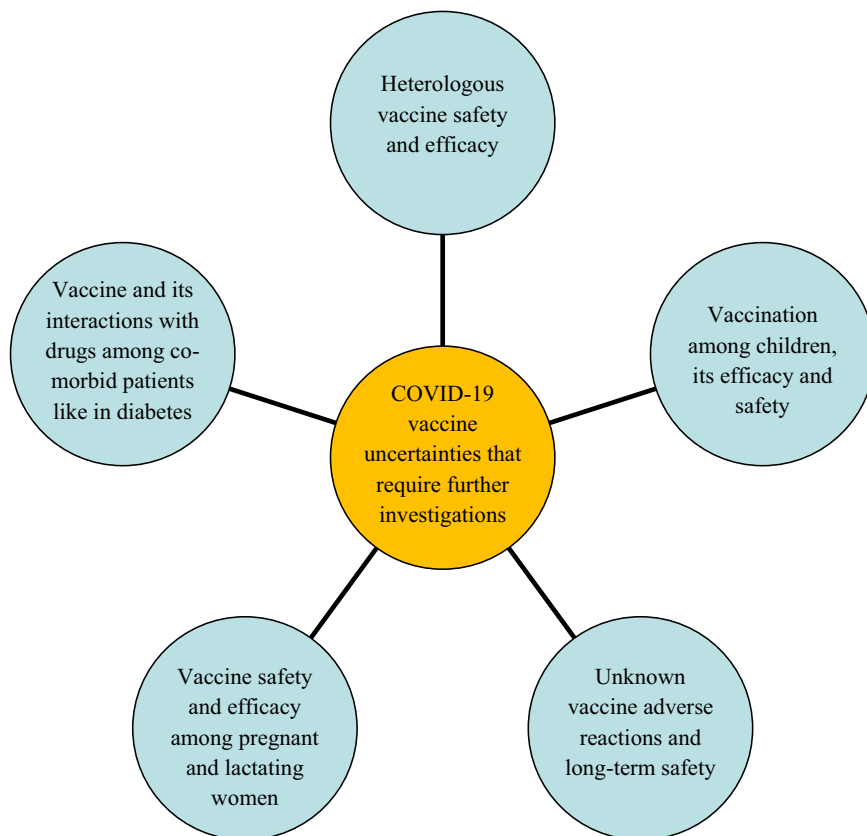
5 | NEED OF NEXT-GEN COVID-19 VACCINES

Populous countries like India are turning into epicenters of particularly lifestyle diseases like hypertension, diabetes, cancer, etc. Thus, issues like vaccine-drug compatibility/relations and adverse reactions if any need to be addressed meticulously to support evidence-based prescription. COVID-19 vaccines reportedly exhibited adverse effects in various forms, particularly among the young. Vaccination nevertheless was recommended by the scientific communities and healthcare professionals despite such observation, with an argument that the benefits of COVID-19 vaccines on target population continue to outweigh the associated risks. However, further evidence of vaccine safety remains to unravel. Emerging SARS-CoV-2 mutants could capably escape neutralizing antibodies rendering the over-the-counter vaccines ineffective.³⁶⁻³⁸ Analysing mutation patterns to facilitate developing mutant-proof, next-gen vaccines against variants seem to be even more rational. The need to work on the significantly mutation-proof, multi-epitopic, next-gen COVID-19 vaccines is emergent.³⁶

6 | FUTURE RESEARCH AND POSSIBLE INTERVENTIONS

Given the fact that most COVID-19 vaccines were approved for emergency use, and many were still in their Phase III/IV trials as they were released for over-the-counter sell, reliable vaccine-safety data is lacking. Vaccine safety especially among children is a major hurdle in successful immunization. A recent report compiled at least 27 cases assessing vaccine safety among babies and adolescents between 6 months and 18 years age-group in 10 countries including India, the United States, and China, with comparatively high adversity rates with mRNA vaccination.³⁹ The European region study noticed higher immunological disorder incidents like multisystem inflammatory syndrome and autoimmune diseases in kids and adolescents.⁴⁰ Based on the available medical literature and published reports, Covishield and Covaxin as inactivated vaccines were recommended

FIGURE 1 Suggested possible future research directions with reference to COVID-19 vaccines.



by the Indian Association of Pediatricians (IAP) and the Academy of Pediatrics Advisory Committee on Vaccination and Immunisation Practices (ACVIP) as safe to administer also to pregnant and lactating/breastfeeding women. Yet, foolproof clinical trials are still needed to be addressed.^{41,42}

The effect of COVID-19 vaccination on comorbid like the diabetic for potential vaccine-drug interactions was explored. Antidiabetic drugs appear to restrict SARS-CoV-2 infection. Among other benefits, these help reduce inflammation and viral replication. Thus, COVID-19 vaccine may be beneficial for the diabetic.⁴³ Contrastingly, antidiabetic medication like insulin and dipeptidyl peptidase-4 inhibitor (DPP-4i) affected the course of COVID-19 and associated mortality adversely.⁴⁴ Even though COVID-19 pandemic has existed for more than 3 years, the emerging novel variants and sub-variants have complicated the issue of combating the pandemic even with the launch of “emergency use” vaccination. Vaccination hesitancy due to the mixed responses wherein individuals either voluntarily accepted or did not receive vaccination could have contributed to the rolling spread with variants and sub-variants. Adverse vaccination experiences like thrombosis with TTS and vaccine-induced immune thrombotic thrombocytopenia (VITT) could have triggered vaccination hesitancy even among the learned or informed section.⁴⁵ Figure 1 depicts the COVID-19 vaccines focussed future research directions in a nutshell.

Cellular and humoral immune responses to both mRNA and viral vector vaccines in the immunodeficient individuals were unprotective, suggesting a heterologous vaccine strategy among such

population.⁴⁶ Yet, heterologous booster dose does not guarantee improved protection, study identifies.⁴⁷ The protection levels of booster dose of various vaccines varied. Vaccine cocktails like bivalent original prototype virus+omicron BA.4/5 subvariants and original prototype virus+omicron BA.1 subvariant vaccine combinations demonstrated positive results in clinical trials, and are approved for human use (<https://healthcare-in-europe.com/en/news/cocktail-vaccines-protect-future-covid-19-variants.html>).

7 | RECOMMENDATIONS

Considering the currently approved commercial vaccines as a panacea against COVID-19 and not considering the adverse fall-outs will indeed be a blunder in the long run. It is high time to instil adequate awareness among healthcare experts engaged in vaccination and the vaccine recipients to acknowledge the signs/symptoms of the associated adversities. Critical TTS and myocarditis cases need serious analyses. Clinicians also should carefully analyse the persistent symptoms like abdominal pain, severe headache, palpitations, dyspnea, etc. post the vaccination till about a week, that are still considered as insignificant medical conditions. The platelet counts and thrombolytic events too need to be closely monitored. These events might be precursors to myocarditis, especially in young males.

As the majority of the current over-the-counter COVID-19 vaccines worldwide are approved for emergency use only, their efficacy and safety features need to be ascertained. There seems to

be a silver-lining in this for the scientific insight in general and clinical trial in particular. That is, the Phase IV (human) clinical trial of these is happening by default with no financial or ethical regulations burden on the vaccine development companies. Taking the advantage, proper documentation, detailed scientific analyses and timely reporting of the adverse fallouts of vaccination may be prioritized to unravel the facts of therapeutic incompatibility and cell-specific interactions. The national-level regulatory agencies may set standard framework to identify, analyse and report all cases with postvaccination adverse clinical symptoms. If need be, an IoT-based national grid may be put on job. Open, transparent and evidence-based communication about the potential benefits and risks of COVID-19 vaccines is essential to ensure trustworthiness. Focused and time-bound collaborative strategy may be tailored for a foolproof understanding of the facts and unveil the molecular mechanism behind vaccine-related adversities. Rigorous studies on the alternate data sources, robust study designs including comparing the vaccinated and nonvaccinated population and a monitoring system for long-term follow-up shall help attaining the prerogatives.

8 | CONCLUSION

The mRNA-based COVID-19 vaccination reported cardiac (myocarditis and pericarditis) complications, mostly after the second dose. Serious blood clot cases and low platelet counts with AstraZeneca and J&J COVID vaccine dosing especially after second dose are reported. Indians experienced throat swelling, breathing difficulty, high blood pressure and convulsion as pathological conditions after Sputnik V vaccination. Considering the currently approved commercial vaccines as the panacea, under-evaluation of the adverse fall-outs will be blunder for sure. Vaccine-associated adverse events are often underreported or are considered as “usually rare,” and the scientific focus for further investigations is lost by design. The Phase IV (human) clinical trial is occurring by default without financially or ethically burdening the concerned companies. A focused and time-bound collaborative strategy to unveil molecular mechanisms of the vaccine-related adverse events may, therefore, be set.

AUTHOR CONTRIBUTIONS

Bhabani Sankar Satapathy: Conceptualization; Data curation; Formal analysis. **Gurudutta Pattnaik:** Data curation; Writing—original draft. **Rudra Narayan Sahoo:** Conceptualization; Formal analysis. **Sovan Pattanaik:** Writing—review & editing. **Ashish K Sarangi:** Conceptualization; Writing—original draft. **Venkataramana Kandi:** Conceptualization; Data curation; Writing—original draft. **Snehasish Mishra:** Writing—original draft. **Ali A Rabaan:** Writing—review & editing. **Aroop Mohanty:** Formal analysis; Writing—review & editing. **Ranjit Sah:** Writing—original draft; Writing—review & editing. **Ranjan K Mohapatra:** Formal analysis; Validation; Writing—original draft; Writing—review & editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No primary data was collected or associated with this article.

TRANSPARENCY STATEMENT

The lead author Ranjit Sah, Ranjan K. Mohapatra affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Venkataramana Kandi  <http://orcid.org/0000-0002-7197-0448>

Ranjit Sah  <http://orcid.org/0000-0002-2695-8714>

Ranjan K. Mohapatra  <http://orcid.org/0000-0001-7623-3343>

REFERENCES

1. Mohapatra RK, Pintilie L, Kandi V, et al. The recent challenges of highly contagious COVID-19, causing respiratory infections: symptoms, diagnosis, transmission, possible vaccines, animal models, and immunotherapy. *Chem Biol Drug Des*. 2020;96(5):1187-1208.
2. Kutikuppala LVS, Kandi V, Sarangi AK, Mishra S, Mohapatra RK. COVID-19 era and the constantly reemerging novel SARS-CoV-2 variants calls for special attention for the geriatrics: a real challenge. *Geriatrics*. 2022;7:143. doi:10.3390/geriatrics7060143
3. Mohapatra RK, Mishra S, Azam M, Dhama K. COVID-19, WHO guidelines, pedagogy, and respite. *Open Med*. 2021;16:491-493.
4. Arumugam VA, Thangavelu S, Fathah Z, et al. COVID-19 and the world with co-morbidities of heart disease, hypertension and diabetes. *J Pure Appl Microbiol*. 2020;14:1623-1638.
5. Shankar VU, Kumar PS, Nirmala K. Epidemiological impact of COVID-19 in India: country with second foremost positive cases in the world. *Total Environ Res Themes*. 2022;3-4:100007.
6. Sarangi A, Javed S, Karki K, Kaushal A. COVID-19-associated PTSD in the elderly—lessons learned for the next global pandemic. *Middle East Current Psychiatry*. 2021;28(1):1-7.
7. Patel SK, Pathak M, Tiwari R, et al. A vaccine is not too far for COVID-19. *J Infect Dev Ctries*. 2020;14:450-453. doi:10.3855/jidc.12744
8. Rabaan AA, Al-Ahmed SH, Sah R, et al. Recent advances in vaccine and immunotherapy for COVID-19. *Hum Vaccin Immunother*. 2020;16(12):3011-3022.
9. Mohapatra RK, Kuppli S, Kumar Suvvari T, et al. SARS-CoV-2 and its variants of concern including Omicron: a never ending pandemic. *Chem Biol Drug Des*. 2022;99:769-788.
10. Shrestha S, Khatri J, Shakya S, et al. Adverse events related to COVID-19 vaccines: the need to strengthen pharmacovigilance monitoring systems. *Drugs Ther Perspect*. 2021;37:376-382.
11. Scobie HM, Edelstein M, Nicol E, et al. Improving the quality and use of immunization and surveillance data: summary report of the working group of the strategic advisory group of experts on immunization. *Vaccine*. 2020;38(46):7183-7197.
12. Dutta S, Kaur RJ, Charan J, et al. Serious adverse events reported from the COVID-19 vaccines: a descriptive study based on WHO database. medRxiv. 2021. doi:10.1101/2021.03.23.21253433
13. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19

- vaccination or SARS-CoV-2 infection. *Nature Med.* 2022;28:410-422.
14. Saeed S, Käsik L, Rajani R, Larsen TH. Incidence, clinical presentation, and management of myocarditis following mRNA-Based Covid-19 vaccines: a brief report. *Cardiology.* 2022;147:406-412.
 15. Karlstad Ø, Hovi P, Husby A, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA Cardiology.* 2022;7:600. doi:10.1001/jamacardio.2022.0583
 16. Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. *The Lancet.* 2022;399:2191-2199. doi:10.1016/S0140-6736(22)00791-7
 17. Ling RR, Ramanathan K, Tan FL, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *The Lancet Respiratory Medicine.* 2022;10:679-688. doi:10.1016/S2213-2600(22)00059-5
 18. Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield). [https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-\(gacvs\)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-\(vaxzevria-and-covishield\)](https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)).
 19. Yaghoubi F, Dalil D. Acquired thrombotic thrombocytopenic purpura after AstraZeneca vaccine: a case report. *Caspian J Intern Med.* 2022;13(suppl 3):299-302. doi:10.22088/cjim.13.0.299
 20. Li X, Burn E, Duarte-Salles T, et al. Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US. *BMJ.* 2022;379:e071594. doi:10.1136/bmj-2022-071594
 21. Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. *The Lancet Haematology.* 2022;9(1):e73-e80. doi:10.1016/S2352-3026(21)00306-9
 22. Sivaramakrishnan P, Mishra M. Vaccination-associated immune thrombocytopenia possibly due to ChAdOx1 nCoV-19 (Covishield) coronavirus vaccine. *BMJ Case Rep.* 2022;15(3):e249237.
 23. Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield) – 16 April 2021. [https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-\(gacvs\)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-\(vaxzevria-and-covishield\)](https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield))
 24. TATA AIG Team, COVID Vaccine Side Effects: Covishield/Covaxin/Sputnik V Side Effects. 2022. <https://www.tataaig.com/knowledge-center/health-insurance/covid-vaccine-side-effects-covishield-covaxin-sputnik>
 25. Agrawal H, Vashishtha H, Debnath I, Agarwal P, Soni R, Mishra R. Public perceptions and experiences with the on-going COVID-19 immunisation programme in India: a survey based study. *J sci temper.* 2022;10(3):140-161.
 26. Coronavirus | 180 deaths following vaccination reported in India. 2021. <https://www.thehindu.com/news/national/coronavirus-180-deaths-following-vaccination-reported-in-india/article34274144.ece>
 27. Selvaraj P, Muthu S, Jeyaraman N, Prajwal GS, Jeyaraman M. Incidence and severity of SARS-CoV-2 virus post COVID-19 vaccination: a cross-sectional study in India. *Clin Epidemiol Glob Health.* 2022;14:100983.
 28. Chaudhary C, Singh M, Khan MNA, Anand BK, Saini S. Adverse events following immunization against COVID-19 among healthcare workers: an observational study in Haryana, India. *Asian J Med Sci.* 2022;13(3):23-29.
 29. Arora G, Taneja J, Bhardwaj P, et al. Adverse events and breakthrough infections associated with COVID-19 vaccination in the Indian population. *J Med Virol.* 2022;94(7):3147-3154.
 30. Bhandari B, Rayamajhi G, Lamichhane P, Shenoy AK. Adverse events following immunization with COVID-19 vaccines: a narrative review. *BioMed Res Int.* 2022;2022:1-11. doi:10.1155/2022/2911333
 31. Veeramreddy NR, Kandi V, Mittal RJ, et al. Adverse effects following COVID-19 vaccination: a state-of-the-art systematic review. *Am J Pharmacol Sci.* 2022;10(1):1-7. doi:10.12691/ajps-10-1-1
 32. Parida SP, Sahu DP, Singh AK, et al. Adverse events following immunization of COVID-19 (Covaxin) vaccine at a tertiary care center of India. *J Med Virol.* 2022;94(6):2453-2459. doi:10.1002/jmv.27655
 33. Das S, Kar SS, Samanta S, Banerjee J, Giri B, Dash SK. Immunogenic and reactogenic efficacy of Covaxin and Covishield: a comparative review. *Immunol Res.* 2022;70(3):289-315.
 34. Mohapatra RK, Sarangi AK, Kandi V, Azam M, Tiwari R, Dhama K. Omicron (B. 1.1. 529 variant of SARS-CoV-2); an emerging threat: current global scenario. *J Med Virol.* 2022;94(5):1780-1783.
 35. Mohapatra RK, El-Shall NA, Tiwari R, et al. Need of booster vaccine doses to counteract the emergence of SARS-CoV-2 variants in the context of the Omicron variant and increasing COVID-19 cases: an update. *Hum Vaccin Immunother.* 2022;18(5):2065824. doi:10.1080/21645515.2022.2065824
 36. Chakraborty C, Bhattacharya M, Sharma AR, et al. Immediate need for next-generation and mutation-proof vaccine to protect against current emerging Omicron sublineages and future SARS-CoV-2 variants: an urgent call for researchers and vaccine companies. *Int J Surg.* 2022;106:106903.
 37. Mohapatra RK, Mahal A, Kutikuppala LS, et al. Renewed global threat by the novel SARS-CoV-2 variants 'XBB, BF.7, BQ.1, BA.2.75, BA.4.6': a discussion. *Front Virol.* 2022;2:1077155. doi:10.3389/fviro.2022.1077155
 38. Mohapatra RK, Verma S, Kandi V, et al. The SARS-CoV-2 omicron variant and its multiple sub-lineages: transmissibility, vaccine development, antiviral drugs, monoclonal antibodies, and strategies for infection control – a review. *Chemistry Select.* 2023;8:e202201380.
 39. Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med.* 2021;385(24):2241-2251. doi:10.1056/NEJMoa2109522
 40. Bizjak M, Emeršič N, Zajc Avramović M, et al. High incidence of multisystem inflammatory syndrome and other autoimmune diseases after SARS-CoV-2 infection compared to COVID-19 vaccination in children and adolescents in south central Europe. *Clin Exp Rheumatol.* 2023;41(5):1183-1191. doi:10.55563/clinexp Rheumatol/i112xn
 41. Kasi SG, Dhir SK, Shivananda S, et al. Breastfeeding and coronavirus disease 2019 (COVID-19) vaccination: position statement of Indian academy of pediatrics advisory committee on vaccination and immunization practices. *Indian Pediatr.* 2021;58(7):647-649. doi:10.1007/s13312-021-2261-z
 42. Adhikari EH, Spong CY. COVID-19 vaccination in pregnant and lactating women. *JAMA.* 2021;325(11):1039-1040. doi:10.1001/jama.2021.1658
 43. Chee YJ, Tan SK, Yeoh E. Dissecting the interaction between COVID-19 and diabetes mellitus. *J Diabetes Investig.* 2020;11(5):1104-1114. doi:10.1111/jdi.13326
 44. Nguyen NN, Ho DS, Nguyen HS, et al. Preadmission use of antidiabetic medications and mortality among patients with COVID-19 having type 2 diabetes: a meta-analysis. *Metabolism.* 2022;131:155196. doi:10.1016/j.metabol.2022.155196

45. Jain N, Chaudhary P, Shrivastava A, et al. Thrombosis with thrombocytopenia syndrome (TTS) after ChAdOx1 nCoV-19 immunization: an investigative case report. *Am J Case Rep.* 2023;24:e938878. doi:10.12659/AJCR.938878
46. Aguinam ET, Nadesalingam A, Chan A, et al. Differential T-cell and antibody responses induced by mRNA versus adenoviral vectored COVID-19 vaccines in patients with immunodeficiencies. *J Allergy Clin Immunol.* 2023;2(2):100091. doi:10.1016/j.jacig.2023.100091
47. Letafati A, Eyvazzadeh N, Gharekhani A, et al. Comparison of AstraZeneca and sinopharm vaccines as boosters in protection

against COVID-19 infection. *Biologicals.* 2023;82:101668. doi:10.1016/j.biologicals.2023.101668

How to cite this article: Satapathy BS, Pattnaik G, Sahoo RN, et al. COVID-19 vaccines and their underbelly: Are we going the right way? *Health Sci Rep.* 2023;6:e1540. doi:10.1002/hsr2.1540