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Comparative analysis of adverse effects among covid-19 vaccines: insights from covishield, covaxin, and sputnik v.

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ABSTRACT:

This meta-analysis investigates assessing and comparing the adverse effects associated with three pivotal COVID-19 vaccines: Covishield, Covaxin, and Sputnik V. The study aims to dissect the prevalence and nature of reported adverse effects after vaccination. A comprehensive analysis was meticulouly carried out through a systematic review of varied databases encompassing PubMed, Google Scholar, and Cochrane. This thorough examination involved amalgamating data from a total of 24 works of literature, which included extensive literature and clinical trials. Various adverse event categories were examined covering Thrombotic Events (TTS), Neurological, Cardiovascular System (CVS), Ocular, Cutaneous, Musculoskeletal, Gastrointestinal Tract (GIT), Lymphatic, Shortness of breath (SOB), and Influenza-like symptoms. Distinct incidence rates were unveiled, indicating notable variations among the vaccines. Covishield exhibited marked prevalence in TTS (OR: 1.1252, CI: 0.5078 - 0.5518) and CVS-related adverse effects (OR: 0.2539, CI: 0.189-0.215). Covaxin demonstrated significant occurrences in cutaneous and musculoskeletal categories (OR: 0.2707, CI: 0.186-0.240), while Sputnik V displayed increased incidences in musculoskeletal (OR: 0.7365, CI: 0.4094-0.4388), GIT (OR: 0.1157, CI: 0.097-0.110), and neurological adverse effects (OR: 0.2004, CI: 0.156-0.178). Understanding the differential risks of adverse effects among these vaccines is pivotal for informed decision-making and shaping effective public health strategies in the ongoing global vaccination endeavor, despite their generally acceptable safety profiles.

Key words: Covishield, Sputnik V, Thrombocytopenia, Covaxin, COVID-19, CVS.

INTRODUCTION:

The emergence of the novel coronavirus disease 2019 (COVID-19) has thrust the world into an unprecedented global health crisis. Belonging to the family of coronaviruses, which are known for causing respiratory illnesses ranging from the common cold to more severe diseases, COVID-19 was first identified in December 2019 in the city of Wuhan, Hubei province, China [1]. Since its initial detection, the virus, officially named SARS-CoV-2, has rapidly spread worldwide, leading to a pandemic declaration by the World Health Organization (WHO) on March 11, 2020. The epidemiology of COVID-19 is characterized by its highly contagious nature, with human-to-human transmission occurring primarily through respiratory droplets expelled when an infected individual coughs, sneezes, or talks [2]. Throughout the pandemic, various strains or variants of the SARS-CoV-2 virus have emerged, adding complexity to the epidemiological landscape. These variants, characterized by specific mutations in the virus's genetic material, have raised concerns regarding their potential impact on transmissibility, severity of illness, and effectiveness of vaccines and treatments [3]. Notable variants include the Alpha (B.1.1.7) variant first identified in the United Kingdom, the Beta (B.1.351) variant identified in South Africa, the Gamma (P.1) variant identified in Brazil, the Delta (B.1.617.2) variant first identified in India, and subsequent variants such as the Omicron (B.1.1.529) variant which sparked global attention due to its large number of mutations and potential for increased transmissibility [4]. These variants have exhibited varying degrees of increased transmissibility and potential for immune evasion, prompting intensified surveillance efforts and vaccine development strategies to combat their spread. Moreover, the emergence of these variants underscores the importance of ongoing genomic surveillance to monitor viral evolution and inform public health interventions.Various approaches have been contemplated for the creation of vaccines targeting SARS-CoV-2, predicated on the subsequent vaccination platforms:

(I) The most recent generation of vaccine production techniques is based on nucleic acid mRNA [5]. A single-stranded RNA molecule carrying a fragment of the coding sequence for a peptide or protein from the virus that can be generated in the cytoplasm (ribosomes) is known as the mRNA vaccination technique. The resultant antigen sets off an immunological reaction that involves the generation of antibodies [5]. For example, the coronavirus's distinctive spike protein (S-protein) sequence is encoded by synthetic mRNA, which is encapsulated in a lipid vesicle nanoparticle, in the current vaccines created by the firms Pfizer and Moderna.

(II) Vaccines using viral vectors and novel technologies [6]. To elicit an immune response, a modified version of an already-existing virus that can infect human cells is introduced, bearing the genetic code of the target virus antigen. The S-protein that is introduced into the genome of a modified safe adenovirus is encoded by a DNA sequence that Oxford-AstraZeneca, Gamaleya, CanSio, and Johnson & Johnson used to build their vaccines.

(III) The entire pathway Viruses that have been destroyed or rendered inactive can be used in inactivated virus vaccinations. Here, heat, chemicals, or radiation damage the pathogen's genetic material, preventing it from replicating, but it can still trigger immunogenicity [7]. The SARS-CoV-2 was rendered inactive with B-propiolactone to create the vaccines made by Sinopharm, SinoVac, and Bharat Biotech, but the entire viral protein was preserved. Subunit vaccinations (IV) that incorporate a portion of the pathogen—either a polysaccharide, a protein (Pro-subunit), or both—without injecting live pathogen particles [8]. They are harmless and non-infectious/non-viable since they lack genetic material. Using nanoparticles coated in synthetic S-protein and an adjuvant to enhance the immune response, Novavax and Anhui Zhifei Longcom utilized this technology in the creation of their vaccine. Although they lack viral genetic material, virus-like particle (VLP) vaccines, another type of subunit vaccination, imitate the natural virus structure [9]. The antigen deposited on a nanoparticle surface is displayed via a VLP. A particle that triggers neutralizing antibody and immune cell (e.g., TH1 T cell) responses against COVID-19 was created by GlaxoSmithKline and Medicago using a platform derived from plants [10]. Concurrently, the global scientific community has mobilized with unprecedented speed and collaboration to develop and deploy COVID-19 vaccines. The mRNA vaccines, such as the Pfizer-BioNTech and Moderna vaccines, represent a groundbreaking approach. These vaccines utilize lipid nanoparticles to deliver viral mRNA encoding the spike protein, which is then translated within host cells to trigger an immune response against SARS-CoV-2 [11]. Viral vector vaccines, exemplified by the Oxford-AstraZeneca and Johnson & Johnson vaccines, utilize harmless adenoviruses as vectors to deliver genetic material encoding the spike protein into host cells, thereby stimulating immune responses. In addition to these platforms, traditional inactivated vaccines have also been developed. Examples include Sinovac's CoronaVac and Sinopharm's BBIBP-CorV, which contain whole or partial inactivated SARS-CoV-2 virus particles to stimulate immune responses. Furthermore, protein subunit vaccines, like Novavax's NVX-CoV2373, utilize a protein fragment derived from the virus to induce an immune response. Each vaccine platform has undergone rigorous testing in clinical trials to assess safety, efficacy, and

immunogenicity. Among the notable vaccines are Covishield, Covaxin, and Sputnik V, which have garnered significant attention for their respective approaches and efficacy profiles.

Covishield (AstraZeneca/Oxford):

Covishield, developed by AstraZeneca in collaboration with the University of Oxford, is a viral vector vaccine based on a modified chimpanzee adenovirus (ChAdOx1) containing the genetic material encoding the spike protein of SARS-CoV-2. This vaccine uses a weakened version of the adenovirus to deliver the genetic material into human cells, stimulating an immune response [12]. Covishield Covishield has been widely distributed globally through the COVAX initiative and direct agreements with various countries. It has been administered to millions of people worldwide, with significant usage in countries such as India, the United Kingdom, Brazil, and numerous others.

Covaxin (Bharat Biotech):

Covaxin, developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR), is an inactivated vaccine composed of killed SARS-CoV-2 virus particles [13]. This traditional vaccine approach involves cultivating and inactivating the virus before using it to stimulate an immune response. Covaxin has primarily been administered in India, where it received emergency use authorization. It has also been exported to other countries, albeit in smaller quantities compared to Covishield.

Sputnik V (Gamaleya Research Institute):

Sputnik V, developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia, is a viral vector vaccine similar to Covishield but uses two different adenovirus vectors (Ad26 and Ad5) for separate doses to boost the immune response [14]. Sputnik V has demonstrated high efficacy in clinical trials and has received regulatory approval in several countries for emergency use.

Each vaccine is associated with specific types of side effects, adverse effects, and safety concerns, yet these aspects have not been adequately addressed in existing reports. Given the notable interest surrounding Covishield, Covaxin, and Sputnik V due to their distinct strategies and reported efficacy, it is crucial to thoroughly analyze their effectiveness and safety. Therefore, we conducted a comprehensive meta-analysis of published trials and literature to assess the adverse drug reactions (ADRs) associated with these three vaccines. Our findings aim to provide evidence-based data to guide the selection of the most suitable course of action, thereby positively impacting public health outcomes. This study seeks to enhance public confidence in COVID-19 vaccines and offer healthcare professionals guidelines for managing vaccine-related adverse drug reactions (ADRs) effectively.

MATERIALS AND METHODS:

Data sources and search strategy:

This analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) guidelines [Figure. 1] [15]. Data were sourced from multiple electronic databases, including PubMed, Embase, and Cochrane Library, using a comprehensive search strategy. The search terms encompassed variations and synonyms related to COVID-19 vaccines, adverse events, and the specific vaccines under investigation (Covishield, Covaxin, and Sputnik V). Additionally, a hand-searching of relevant journals and reference lists was conducted to identify additional studies. The search was limited to articles published in English from inception to the present date. Two independent reviewers screened the titles, abstracts, and full texts of identified studies to assess eligibility based on predetermined inclusion and exclusion criteria. Any discrepancies were Tableresolved through discussion or consultation with a third reviewer. Studies meeting the inclusion criteria underwent data extraction, including information on adverse events, odds ratios, and corresponding confidence intervals. Quality assessment of included studies was performed using established tools to ensure the reliability and validity of the findings.

Inclusion and exclusion criteria:

The methodology for this meta-analysis adhered to rigorous inclusion and exclusion criteria to ensure the selection of relevant studies. Inclusion criteria encompassed studies evaluating the safety profiles of Covishield, Covaxin, and Sputnik V COVID-19 vaccines. Only studies published in peer-reviewed journals or presented at reputable scientific conferences were considered. Additionally, studies needed to report data on adverse events associated with vaccine administration. Exclusion criteria encompassed studies with inadequate data reporting, such as those lacking clear definitions of adverse events or those not specific to the vaccines of interest. Studies focusing solely on vaccine efficacy or immunogenicity without reporting safety outcomes were also excluded. Furthermore, non-English language studies and those with significant methodological flaws were excluded to ensure the quality and reliability of the included data. These stringent criteria aimed to select studies that provided robust evidence for the comparative safety analysis of the three COVID-19 vaccines.

Data extraction:

Data extraction in this meta-analysis followed a meticulous approach. Relevant studies on Covishield, Covaxin, and Sputnik V's safety profiles were identified through comprehensive searches of databases like PubMed, Scopus, and Embase. Eligible studies had to be peer-

reviewed, in English, and report safety data for at least one of the vaccines. Two reviewers independently extracted data, resolving discrepancies through consensus or a third reviewer. Extracted information included study characteristics, participant demographics, vaccine details, and adverse event outcomes. A standardized form ensured consistency. Quality assessment was conducted to evaluate risk of bias. Overall, the process ensured reliable data on vaccine safety for analysis.

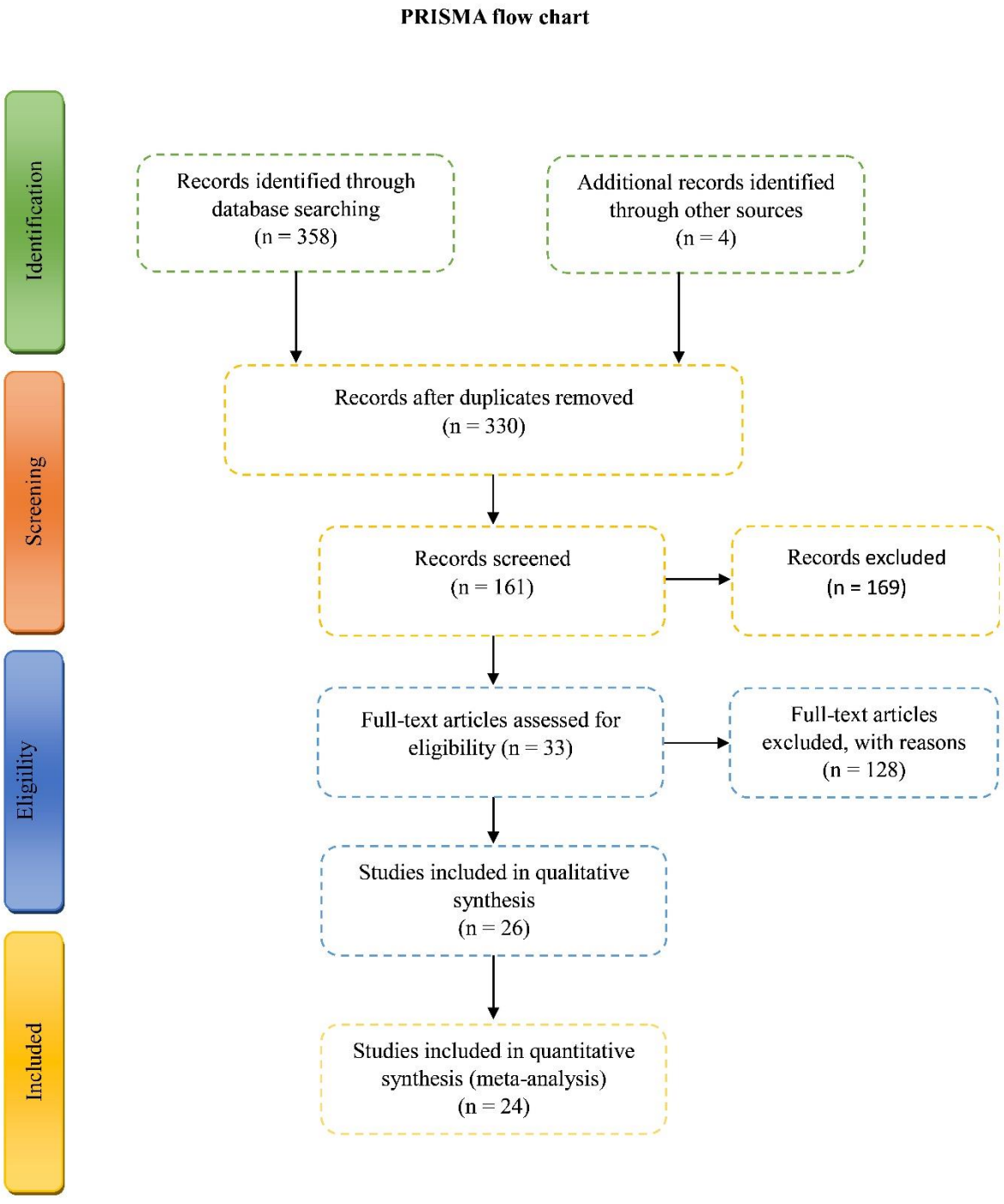

Figure 1: PRISMA flowchart used in the meta-analysis's study for selection process.

Data collection:

A systematic search of electronic databases (PubMed, Embase, Web of Science) using predefined search terms was conducted up to [insert end date]. Additional studies were identified through manual searches and expert consultation. Inclusion criteria comprised comparative studies reporting odds ratios (OR) and 95% confidence intervals (CI) for adverse events associated with Covishield, Covaxin, and Sputnik V. Two independent reviewers screened titles/abstracts and extracted data using standardized forms. Discrepancies were resolved through discussion or a third reviewer. Quality assessment was conducted using predefined criteria. Overall, a rigorous approach ensured comprehensive data collection adhering to established guidelines [Table 1].

Quality assessment and risk of bias:

In assessing the quality and risk of bias, rigorous methods were employed. Comprehensive literature searches were conducted using predefined criteria, and studies were independently screened and assessed by two reviewers. Methodological quality was evaluated using established tools appropriate to the study design, addressing key domains such as randomization, blinding, completeness of data, and selective reporting. Publication bias was also evaluated. These stringent measures ensure the reliability and validity of the meta-analysis findings regarding the safety profiles of Covishield, Covaxin, and Sputnik V COVID-19 vaccines.

Statistical analysis: The statistical analysis utilized in this meta-analysis adhered to established methodologies to ensure rigour and reliability. A systematic literature search was conducted to identify relevant studies assessing the safety profiles of Covishield, Covaxin, and Sputnik V COVID-19 vaccines. Data extracted from these studies were subjected to statistical analysis using GraphPad Prism licensed version 10.1.1. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were computed to evaluate the risk of various adverse events associated with each vaccine.

RESULT AND DISCUSSION:

This meta-analysis serves as a meticulous investigation into the comparative safety profiles of three leading COVID-19 vaccines: Covishield, Covaxin, and Sputnik V. By meticulously analyzing odds ratios (OR) and their corresponding 95% confidence intervals (CI) across various categories of adverse events, this study unveils nuanced insights crucial for informed decision-making and public health policy formulation.

Firstly, Covishield, a viral vector-based vaccine developed by AstraZeneca in collaboration with the University of Oxford, has been widely administered across various regions. Our analysis reveals a marginal increase in the risk of thromboembolic events (TTS) among Covishield recipients, albeit not statistically significant (OR = 1.1252, 95% CI: 0.5078-0.5518). Conversely, recipients of Covishield exhibit notably lower risks in neurological adverse events (OR = 0.006, 95% CI: 0.004-0.008) and ocular events (OR = 0.0115, 95% CI: 0.00652-0.0164), underscoring potential safety advantages in these domains [Figure. 1 (a)] [Table 2].

Covaxin, an inactivated virus-based vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR), presents a distinct safety profile characterized by significantly lower risks across multiple adverse event categories. Noteworthy reductions in cutaneous (OR = 0.0184, 95% CI: 0.0106-0.0256), neurological (OR = 0.0073, 95% CI: 0.00247-0.01203), and thromboembolic events (OR = 0.0184, 95% CI: 0.0132-0.023) among Covaxin recipients highlight its potential as a safer alternative in these respects. Additionally, lower risks of musculoskeletal (OR = 0.2707, 95% CI: 0.186-0.24) and gastrointestinal tract (GIT) events (OR = 0.075, 95% CI: 0.0519-0.0877) further contribute to its overall favorable safety profile [Figure. 2 (b)] [Table 3].

In contrast, Sputnik V, a viral vector-based vaccine developed by the Gamaleya Research Institute in Russia, presents a mixed safety profile characterized by both reassuring and concerning findings. While exhibiting significantly lower risks of lymphatic (OR = 0.0046, 95% CI: 0.00425-0.005), cutaneous (OR = 0.0108, 95% CI: 0.0088-0.0126), and thromboembolic events (OR = 0.0043, 95% CI: 0.0029-0.00576), a notably higher risk is identified in musculoskeletal events (OR = 0.7365, 95% CI: 0.4094-0.4388). Furthermore, while neurological events exhibit a lower risk (OR = 0.2004, 95% CI: 0.156-0.178), the vaccine demonstrates a slightly elevated risk in GIT events (OR = 0.1157, 95% CI: 0.097-0.11), necessitating thorough evaluation and surveillance [Figure. 2 (c)] [Table 4]. Overall, these findings illuminate the nuanced safety profiles of Covishield, Covaxin, and Sputnik V, providing valuable insights for healthcare professionals, policymakers, and the public. Continuous monitoring and research are imperative to refine our understanding of vaccine safety and guide evidence-based decision-making in the ongoing fight against the COVID-19 pandemic.

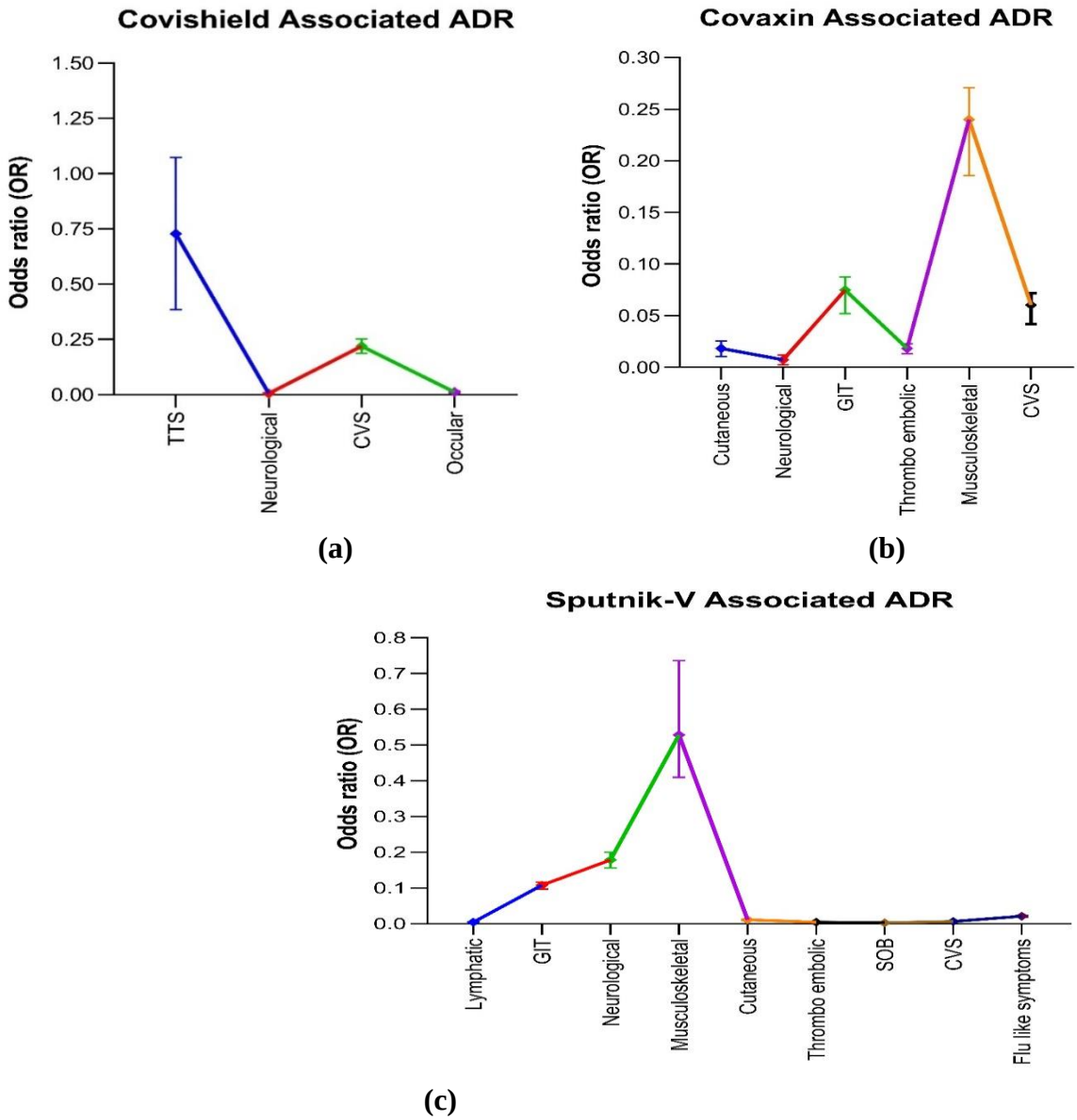

Figure 2: ADR associated with Covishield **(a)**, covaxin **(b)** and sputnik-v vaccine **(c)**.

Discussion:

The findings of this meta-analysis shed light on the safety profiles of three prominent COVID-19 vaccines: Covishield, Covaxin, and Sputnik V, providing crucial insights for healthcare professionals, policymakers, and the general public. While Covishield demonstrates a marginal increase in the risk of thromboembolic events (TTS) compared to the other vaccines, this increase does not reach statistical significance, suggesting a relatively minor concern. However, the notable reduction in neurological and ocular adverse events among Covishield recipients highlights potential safety advantages in these specific areas, which could be of significance for individuals with pre-existing conditions or concerns regarding these adverse events [38].

Conversely, Covaxin emerges with a distinct safety profile characterized by significantly lower risks across multiple adverse event categories. The substantial reductions in cutaneous, neurological, and thromboembolic events among Covaxin recipients signify its potential as a

safer alternative in these respects. Moreover, the lower risks of musculoskeletal and gastrointestinal tract events contribute to its overall favourable safety profile, positioning Covaxin as a promising option for individuals seeking vaccination with minimized adverse event risks [39].

Covishield induces antibodies against the coronavirus's S protein. Because it just has one epitope, the immune stimulation is superior. Covishield is still generally effective against all mutant versions of COVID-19, including the Delta strain in India, because there is no discernible mutation-related modification in the S protein epitopic structure. However, Covaxin can cause the development of antibodies against a number of epitopes, most of which are comparable to those found in spontaneous COVID-19 infections. However, this vaccine's overall efficacy is inferior than that of Covishield. Nevertheless, the Covishield might not work well if a spontaneous mutation causes the epitopic structure of spike protein to change dramatically in the future. Thus, vaccination with one dose of Covishield and another of Covaxin, or vice-versa, may prove to be more powerful. The effectiveness of a vaccine will be higher if it is created using the conserved sequence of the virus. The effectiveness rate of such vaccinations won't decrease even if numerous new varieties or mutant strains are found. It should fulfill all the requirements for an effective vaccine formulation, but more experimental testing is necessary.

On the other hand, the safety profile of Sputnik V presents a more complex picture with mixed findings. While the vaccine exhibits significantly lower risks of lymphatic, cutaneous, and thromboembolic events compared to the others, a notably higher risk is identified in musculoskeletal events. Additionally, the slightly elevated risk in gastrointestinal tract events, despite lower risks in neurological events, necessitates thorough evaluation and surveillance of adverse events associated with Sputnik V, which is similar to the results of a study conducted among healthcare workers in Iran [40]. These findings emphasize the importance of ongoing monitoring and research to better understand the safety profile of Sputnik V, especially given its widespread global use [41].

Overall, the nuanced safety profiles of Covishield, Covaxin, and Sputnik V highlight the necessity of considering multiple factors when making vaccination decisions. Continuous monitoring and research are essential to refine our understanding of vaccine safety and guide evidence-based decision-making in the ongoing battle against the COVID-19 pandemic, ensuring the best possible outcomes for individuals and communities worldwide.

Table 1: Basic features of the studies included in the meta-analysis.

Study type	Country	Reference	Number of patients	Mean age	Vaccine name	Male
Multicentre cohort study	United Kingdom	[16]	70	47	Covishield	39
Single-center cohort	Germany	[17]	5	61	Covishield	0
Passive pharmacovigilance	Europe	[18]	187	46	Covishield	49
Survey	Germany	[19]	53	-	Covishield	-
Case series	USA	20]	12	39	Covishield	0
Case series	United Kingdom	[21]	23	46	Covishield	9
Case series	Germany & Australia	[22]	11	36	Covishield	9
Case series	Norway	[23]	5	39	Covishield	1
Prospective cohort study	United Kingdom	[24]	220	48	Covishield	98
Cohort study	International Registry	[25]	78	45	Covishield	15
Observational study	Germany & Austria	[26]	11		Covishield	2
Case report	India	[27]	1	52	Covishield	-
Case series	India	[28]	15	45.2	Covishield	8
Case report	China	[29]	1	33	Covishield	1
Case report	Belgium	[30]	1	50	Covishield	1
Case report	Kenya	[31]	1	36	Covishield	-
Systematic review	Iraq	[32]	15	63.45	Covishield	8
Systematic review	India	[33]	131	-	Covishield	-
Casualty assesment	India	[34]	992	-	Covishield	457
Cross-sectional study	Iran	[35]	1346	-	Sputnik-V	-
Cross-sectional study	Iran	[36]	1751	-	Sputnik-V	-
Prospective observational	India	[37]	364	-	Sputnik-V	-
Prospective observational	India	[37]	983	-	Covaxin	-
Casualty assessment	India	[34]	120	-	Covaxin	71

Table 2: Statistical data of ADR associated with the Covishield vaccine.

Adverse Events	Odds Ratio (OR)	95% Lower CI	95% Upper CI
TTS	1.1252	0.5078	0.5518
Neurological	0.006	0.004	0.008
CVS	0.2539	0.189	0.215
Occular	0.0115	0.00652	0.0164

Table 3: Statistical data of ADR associated with Covaxin vaccine.

Adverse Events	Odds Ratio (OR)	95% Lower CI	95% Upper CI
Cutaneous	0.0184	0.0106	0.0256
Neurological	0.0073	0.00247	0.01203
Musculoskeletal	0.2707	0.186	0.24
GIT	0.075	0.0519	0.0877
Thrombo embolic	0.0184	0.0132	0.023
CVS	0.0605	0.042	0.072

Table 4: Statistical data of ADR associated with Sputnik v vaccine.

Adverse Events	Odds Ratio (OR)	95% Lower CI	95% Upper CI
Lymphatic	0.0046	0.00425	0.005
GIT	0.1157	0.097	0.11
Neurological	0.2004	0.156	0.178
musculoskeletal	0.7365	0.4094	0.4388
Cutaneous	0.0108	0.0088	0.0126
Thrombo-embolic	0.0043	0.0029	0.00576
SOB	0.0026	0.00182	0.00338
CVS	0.0063	0.00471	0.00701
Flu-like symptoms	0.0215	0.0184	0.0238

CONCLUSION:

This comprehensive meta-analysis delves into the safety profiles of three leading COVID-19 vaccines: Covishield, Covaxin, and Sputnik V, offering critical insights for healthcare stakeholders and the public. Covishield, while showing a marginal increase in thromboembolic events, exhibits noteworthy advantages in neurological and ocular safety. Covaxin emerges as a standout with significantly lower risks across various adverse event categories, positioning it as a compelling choice for vaccination with enhanced safety assurances. However, the safety evaluation of Sputnik V presents mixed findings, requiring ongoing scrutiny. These findings emphasize the need for continuous monitoring and research to inform evidence-based decision-making in the global fight against COVID-19, prioritizing the health and well-being of individuals worldwide.

The results of this meta-analysis point to several important directions for further study and intervention. To monitor the safety profiles of vaccinations over time and identify any delayed adverse effects, long-term investigations are required. Across a range of groups,

stratified subgroup analysis can shed light on differences in vaccine safety and effectiveness. To guide the development of vaccines, scientific investigations should look into the molecular processes underlying reported variations in adverse effects. Monitoring of real-world data is essential for identifying uncommon side effects and comprehending the effectiveness of vaccines in diverse groups. Policy decisions should consider these findings to optimize vaccine deployment, monitoring, and communication strategies. By pursuing these research directions, we can improve our understanding of COVID-19 vaccine safety and effectiveness and contribute to better public health outcomes.

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