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TAISE FERREIRA CAVALCANTE

SITUAÇÃO VACINAL DOS PACIENTES INTERNADOS POR COVID-19 DURANTE A ONDA ÔMICRON BQ.1.1 EM ARACAJU, SERGIPE, BRASIL

ARACAJU

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Sergipe como requisito à obtenção do grau de Mestre em Ciências da Saúde.

Orientador: Prof. Dr. Paulo Ricardo Martins Filho

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RESUMO

SITUAÇÃO VACINAL DOS PACIENTES INTERNADOS POR COVID-19 DURANTE A ONDA ÔMICRON BQ.1.1 EM ARACAJU, SERGIPE, BRASIL, TAISE FERREIRA CAVALCANTE, ARACAJU, 2023.

A pandemia de COVID-19, ocasionada pelo vírus SARS-CoV-2, continua sendo uma questão primordial para a saúde pública mundial, particularmente com a aparição de novas variantes. Este estudo buscou avaliar a situação vacinal dos pacientes internados durante a onda da variante Ômicron BQ.1.1 em Aracaju, Sergipe. Utilizando uma abordagem ecológica, o estudo analisou dados da Secretaria Municipal da Saúde de Aracaju referentes à hospitalização de adultos por COVID-19 no município de 23 de outubro a 31 de dezembro de 2022. As variáveis examinadas envolviam detalhes demográficos, registros de vacinação, intervalo de tempo entre a última dose da vacina e a internação hospitalar, e tipo de leito. A avaliação dos dados foi conduzida através de uma análise de variância bifatorial (ANOVA), onde foi estabelecido um nível de significância (α) de 0,05. Durante esse período, a taxa de hospitalização pela doença no município foi de 1,6% e 147 adultos hospitalizados devido à COVID-19 foram incluídos neste estudo. Predominantemente, eram idosos (idade média de 77 anos) com comorbidades pré-existentes. A vasta maioria (91,8%) recebeu a série primária de vacinação, com uma parcela significativa tendo recebido doses de reforço adicionais. Notavelmente, 94,8% dos que tomaram duas doses receberam uma terceira, e 61,5% uma quarta dose. Entre os vacinados com quatro doses, 83% tinham 70 anos ou mais, e cerca de 75% receberam a última dose seis meses antes da hospitalização. Observou-se uma interação significativa entre idade avançada e tempo decorrido desde a última dose ($\geq$6 meses) com necessidade de internação em UTI ($p=0,017$). Os resultados apontam que a quarta dose da vacina oferece proteção de curta duração contra formas graves da COVID-19. Salienta-se ainda a necessidade de políticas públicas para promover a administração de uma quarta dose na população adulta e uma quinta dose em pessoas com mais de 70 anos, especialmente se o intervalo da última dose ultrapassar seis meses.

Descritores: COVID-19; SARS-CoV-2; Vacina contra COVID-19.

ABSTRACT

VACCINATION STATUS OF PATIENTS HOSPITALIZED FOR COVID-19 DURING THE ÔMICRON BQ.1.1 WAVE IN ARACAJU, SERGIPE, BRAZIL, TAISE FERREIRA CAVALCANTE, ARACAJU, 2023.

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, remains a key issue for global public health, particularly with the emergence of new variants. This study sought to evaluate the vaccination status of patients hospitalized during the wave of the Ômicron BQ.1.1 variant in Aracaju, Sergipe. Using an ecological approach, the study analyzed data from the Municipal Health Department of Aracaju regarding the hospitalization of adults due to COVID-19 in the municipality from October 23 to December 31, 2022. The variables examined involved demographic details, vaccination records, interval time between the last dose of the vaccine and hospital admission, and type of bed. Data evaluation was conducted using a two-factor analysis of variance (ANOVA), where a significance level (α) of 0.05 was established. During this period, the hospitalization rate for the disease in the city was 1.6% and 147 adults hospitalized due to COVID-19 were included in this study. Predominantly, they were elderly (average age 77 years) with pre-existing comorbidities. The vast majority (91.8%) received the primary vaccination series, with a significant proportion receiving additional booster doses. Notably, 94.8% of those who took two doses received a third, and 61.5% a fourth dose. Among those vaccinated with four doses, 83% were 70 years of age or older, and around 75% received the last dose six months before hospitalization. A significant interaction was observed between advanced age and time elapsed since the last dose ($\geq$6 months) with the need for ICU admission ($p=0.017$). The results indicate that the fourth dose of the vaccine offers short-term protection against severe forms of COVID-19. It is also important to highlight the need for public policies to promote the administration of a fourth dose in the adult population and a fifth dose in people over 70 years of age, especially if the interval between the last dose exceeds six months.

Keywords: COVID-19; SARS-CoV-2; COVID-19 vaccine.

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1 INTRODUÇÃO

A crise da COVID-19 ascendeu rapidamente à uma grave questão de saúde pública em escala global, caracterizada por uma rápida propagação viral, transmissão intensa de pessoa para pessoa e uma notável virulência. Durante sua fase inicial, a falta de antivirais específicos ou vacinas potencializou um alarmante aumento nas taxas de morbidade e mortalidade, além de promover uma significativa desestabilização econômica e social. Nos primeiros três anos da pandemia, de 2020 a 2022, a incidência global de casos de COVID-19 atingiu aproximadamente 83 mil por milhão de habitantes, resultando em uma taxa de mortalidade de 839 por milhão, conforme reportado pela Organização Mundial da Saúde (OMS) (2023).

Esta pandemia ressaltou a necessidade vital de colaboração internacional para combater uma emergência sanitária global. Nações e entidades globais uniram forças para trocar conhecimentos, alinhar iniciativas de pesquisa, acelerar o desenvolvimento de vacinas e terapias, além de estender apoio às regiões mais impactadas. Ficou evidente que uma estratégia coesa e multifacetada por parte das autoridades sanitárias era crucial para mitigar a disseminação do vírus e garantir a segurança das comunidades.

Ao redor do mundo, estratégias de vacinação foram estabelecidas para priorizar a imunização de grupos específicos, determinados por critérios de idade e presença de comorbidades preexistentes. Estas medidas visavam não apenas controlar a proliferação do vírus, mas também reduzir a pressão sobre os serviços de saúde e impulsionar a recuperação econômica. No entanto, apesar do progresso significativo e da crescente consciência global, a emergência de novas variantes do vírus, provenientes de mutações frequentes durante o processo de replicação, permanece como uma preocupação constante, desencadeando discussões sobre potenciais aumentos na patogenicidade das cepas circulantes e da imunidade natural e induzida pela vacina (Jeyanathan et al., 2020).

Os imunizantes desenvolvidos contra a COVID-19 emergiram como a ferramenta mais potente, segura e custo-efetiva para prevenir internações, admissões em unidades de terapia intensiva (UTI) e mortes relacionadas à doença. Num estudo ecológico sobre efeitos adversos associados a doses da COVID-19 em um município brasileiro, Martins-Filho et al. (2022a) apontam que as evidências reforçam a segurança e tolerabilidade à CoronaVac e Oxford-AstraZeneca, utilizadas contra a COVID-19, com apenas 33 eventos adversos por 10.000

doses de vacina durante os primeiros três meses da campanha de vacinação. Além disso, estudo posterior ressaltou o protagonismo da vacinação para prevenir mortes durante o 'tsunami' da Ômicron no Brasil (Martins-Filho et al., 2022b).

No entanto, pesquisas recentes indicam que, embora a vacinação promova uma resposta sustentada das células T ao SARS-CoV-2 (Keeton et al., 2022), há uma redução progressiva na capacidade de neutralizar o vírus ao longo do tempo, enfatizando a necessidade de doses de reforço, principalmente para conferir proteção contra variantes como a Ômicron (Renia et al., 2022). Além disso, estudos revelaram evidências de diminuição da eficácia da vacina em alguns meses após a terceira (Goh et al., 2022) e após a quarta doses (Nordström et al., 2022), bem como a possibilidade de pelo menos uma recorrência de onda de COVID-19 no intervalo de 3 a 9 meses (Cappi et al., 2022), gerando debate sobre a necessidade de doses adicionais em intervalos regulares.

Embora 80% da população brasileira estivesse imunizada contra a COVID-19 com duas doses das vacinas CoronaVac (Sinovac/Butantan), Covishield (Oxford-AstraZeneca/Fiocruz) ComiRNAty (Pfizer/BioNTech) ou Janssen (Johnson & Johnson), com cerca de metade da população recebendo uma dose de reforço, uma quinta onda de COVID-19 impulsionada pela circulação da variante Ômicron BQ.1.1 ocorreu no país no final de 2022, resultando em um aumento significativo de internações e mortes pela doença. Dentro deste cenário, o presente estudo buscou avaliar a situação vacinal dos pacientes internados durante a onda da variante Ômicron BQ.1.1 em Aracaju, Sergipe.

2 OBJETIVOS

2.1 GERAL**:**

a) Avaliar a situação vacinal dos pacientes internados por COVID-19 durante a onda da variante Ômicron BQ.1.1 em Aracaju, Sergipe, Brasil.

2.2 ESPECÍFICOS:

a) Descrever a proporção de pacientes hospitalizados por COVID-19 de acordo com a idade;

b) Descrever a proporção de pacientes hospitalizados com COVID-19 que receberam a quarta dose da vacina;

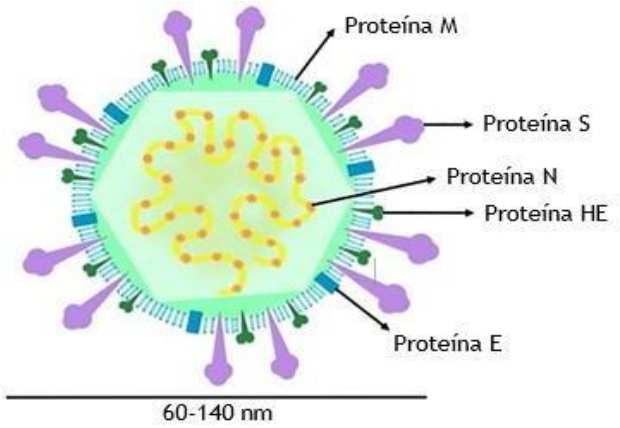
c) Analisar a interação entre idade, intervalo de tempo entre a última dose da vacina e internação hospitalar, e tipo de leito.

3 REVISÃO DA LITERATURA

3.1 O SARS-CoV-2 e a COVID-19

Os coronavírus, como descritos em estudos anteriores (Hageman, 2020), são agentes patogênicos de RNA de fita simples, orientação positiva, e não-segmentados. Estes vírus possuem uma membrana proteica, cujo componente principal é a proteína E. A observação microscópica revela que eles têm uma forma geralmente arredondada ou ovalada, com dimensões que oscilam entre 60 e 140 nm. A superfície desses vírus é caracterizada por projeções significativas que se assemelham a uma coroa, origem da nomenclatura "corona". Estas projeções, como ilustrado na Figura 1, são compostas principalmente de grandes glicoproteínas espículas, conhecidas como proteínas S, que têm um papel crucial na evolução e mutação do vírus (Pires Brito et al., 2020).

Figura 1. Representação gráfica do SARS-CoV-2.



Fonte: Adaptado de Pires Brito et. al (2020).

No final de 2019, uma ameaça surgiu no horizonte global. A COVID-19, causada pelo SARS-CoV-2 (*severe acute respiratory syndrome-associated coronavirus 2*), se manifestou inicialmente como casos de uma pneumonia de etiologia desconhecida em Wuhan, China. O genoma viral foi rapidamente sequenciado, acionando uma resposta científica internacional que tem visto uma evolução notável desde então. No decorrer da pandemia, o vírus sofreu uma série de mutações, resultando em variantes de preocupação, como Alpha, Beta, Gamma e Delta, que afetaram as estratégias de saúde pública global (Zhu et al., 2020).

A emergência da variante Ômicron reacendeu preocupações globais (Torjesen, 2021), dada a sua notável série de mutações, especialmente na região do domínio de ligação ao receptor da proteína S, o que pode potencialmente influenciar a eficácia das vacinas atuais e a transmissibilidade do vírus (Kannan; Ali; Sheza, 2021). As subvariantes desta linhagem têm mostrado diferenças significativas em suas características, cada uma apresentando um perfil mutacional único que pode influenciar a dinâmica da pandemia de formas distintas, incluindo influências no domínio de ligação do receptor (Verma; Subbarao, 2021). Assim, a emergência da variante Ômicron trouxe novos desafios, especialmente no que diz respeito à eficácia das vacinas atuais e a transmissibilidade do vírus. Este cenário ressalta a necessidade de adaptação contínua das estratégias de saúde pública a um patógeno em mudança, incluindo possíveis ajustes nas políticas de vacinação (Kennedy et al., 2020).

A principal rota de transmissão do SARS-CoV-2 é através de gotículas respiratórias, expelidas quando uma pessoa infectada fala, tosse ou espirra. A contaminação indireta, ao entrar em contato com superfícies infectadas seguido de contato com o rosto, também é uma via significativa de transmissão (Ministério da Saúde, 2021). Para conter a propagação do vírus, medidas preventivas eficazes foram promovidas globalmente. Isso inclui a vacinação, uso de máscaras, higiene das mãos e evitar ambientes aglomerados. A ciência tem estado na vanguarda da resposta à pandemia, aprofundando nosso entendimento dos coronavírus humanos e facilitando o desenvolvimento de tratamentos mais eficazes.

Sabemos que o curso clínico da COVID-19 pode variar significativamente entre indivíduos. Muitos experimentam sintomas leves, enquanto outros podem desenvolver complicações sérias, especialmente aqueles com idade avançada ou comorbidades preexistentes. Estudos têm buscado identificar os fatores associados à gravidade e mortalidade da doença, fornecendo *insights* valiosos para o manejo clínico dos pacientes com COVID-19 (Martins-Filho; Tavares; Santos, 2020; Martins-Filho et al., 2021).

Porém, a pandemia também exacerbou desigualdades históricas, com populações vulneráveis sendo desproporcionalmente afetadas. As áreas com maiores desigualdades sociais, culturais e econômicas têm enfrentado desafios adicionais, incluindo acesso limitado a testes e taxas de mortalidade mais elevadas (Martins-Filho et al., 2020). Este complexo mosaico de fatores destaca a necessidade de uma resposta multifacetada à pandemia, que aborde não apenas as implicações médicas, mas também os profundos impactos sociais e econômicos da COVID-19 (Ribeiro et al., 2021).

3.2 Subvariantes Ômicron sob monitoramento

A OMS acompanha as subvariantes do SARS-CoV-2 por meio de uma rede global de vigilância genômica e epidemiológica. Essa rede é composta por laboratórios de todo o mundo que sequenciam o genoma do vírus em amostras coletadas de pacientes com COVID-19, obedecendo as seguintes etapas:

1. Sequenciamento Genômico: Os laboratórios em todo o mundo realizam o sequenciamento do genoma do vírus em amostras de pacientes com COVID-19. Isso envolve a identificação das sequências genéticas específicas que compõem o vírus, permitindo a detecção de mutações e a identificação de novas subvariantes.

2. Compartilhamento de Dados: Os dados de sequenciamento genômico são compartilhados internacionalmente por meio de iniciativas como o GISAID (Iniciativa Global de Compartilhamento de Dados sobre Gripe). Isso permite que os pesquisadores e a comunidade global de saúde acompanhem a disseminação das subvariantes.

3. Análise de Mutações: A OMS e seus parceiros realizam análises detalhadas das mutações identificadas nas subvariantes para determinar seu potencial impacto na transmissibilidade, gravidade da doença e eficácia das vacinas e tratamentos.

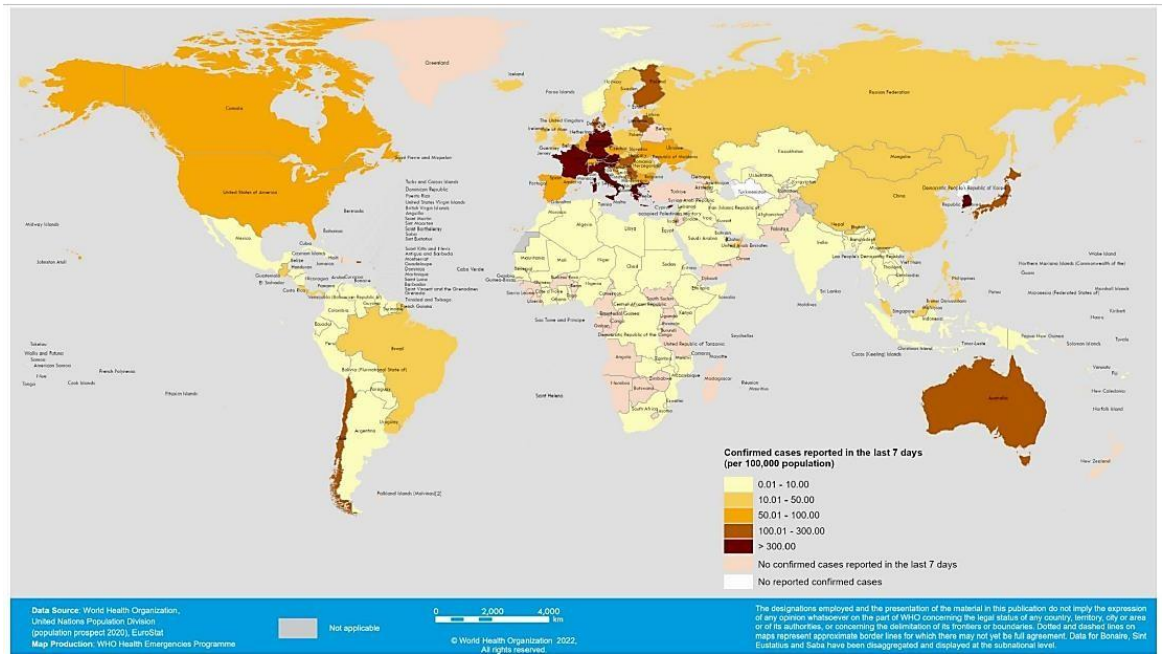
4. Classificação e Nomeação: Inclui o desenvolvimento de sistemas de classificação e nomenclatura para as subvariantes com base em suas características genéticas e epidemiológicas.

5. Comunicação e Atualização: Inclui a comunicação regular das descobertas sobre subvariantes, suas implicações e orientações relevantes para a comunidade global.

O monitoramento contínuo das subvariantes é fundamental para entender a evolução do vírus, adaptar estratégias de controle da pandemia e avaliar a eficácia das medidas de saúde pública, como a vacinação. O compartilhamento global de dados e a colaboração entre países e organizações desempenham um papel crucial nesse processo.

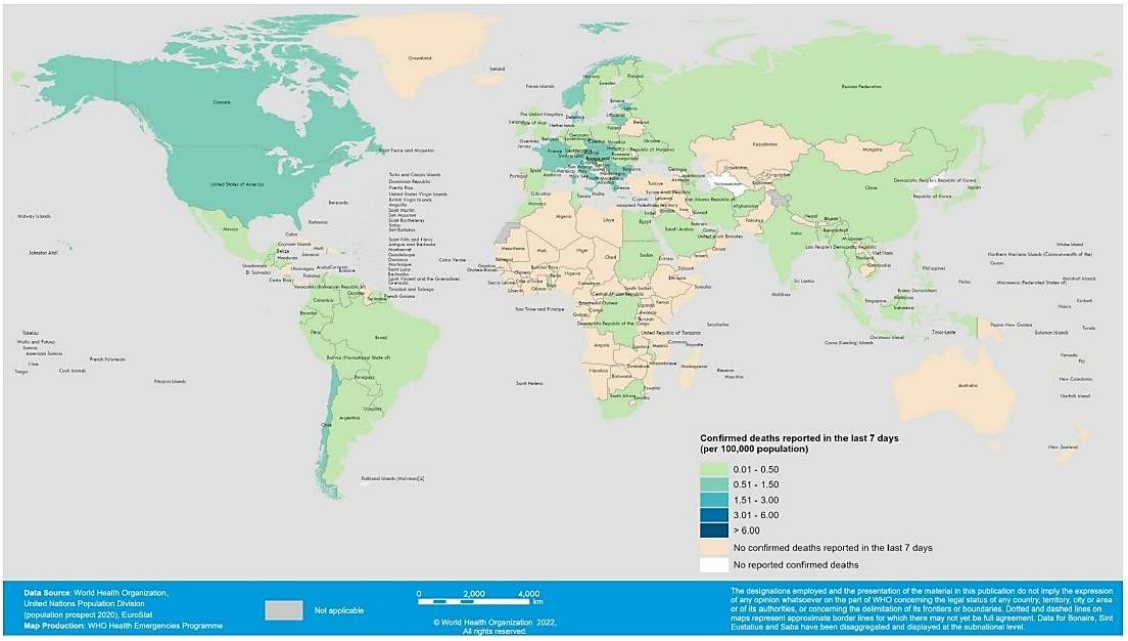
A Figura 2 mostra que durante a semana epidemiológica 42 de 2022, que ocorreu de 16 a 22 de outubro de 2022, observou-se a disseminação global das variantes BQ.1 e BA.5. A BQ.1 registrou um aumento significativo, passando de 9,4% para 13,4%, enquanto a BA.5 com mutações adicionais (R346X, K444X, V445X, N450D e/ou N460X) aumentou de 20,8% para 22,9%, principalmente devido à presença da mutação BA.5 + R346X. Além disso, o XBB e suas variantes descendentes subiram de 1,1% para 2,0% (OMS, 2022).

Figura 2. Casos de COVID-19 por 100.000 habitantes notificados por países, territórios e áreas, SE 42/2022, 16 a 22 de outubro de 2022.



Fonte: https://covid19.who.int/ COVID-19 Weekly Epidemiological Update, Ed.115, 2022.

Figura 3. Morte por COVID-19 por 100.000 habitantes notificados por países, territórios e áreas, SE 42/2022, 16 a 22 de outubro de 2022.



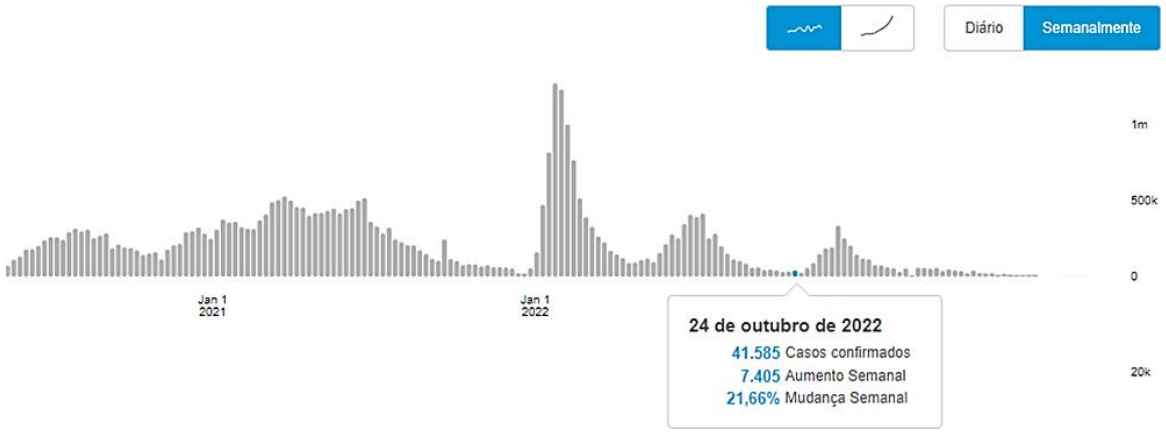
Fonte: https://covid19.who.int/ COVID-19 Weekly Epidemiological Update, Ed.115, 2022.

A Figura 3 mostra que durante a semana epidemiológica 42 de 2022, os maiores números de mortes semanais ocorreram nos Estados Unidos da América, na Federação Russa, na Itália , França e China.

Além disso, No Brasil, por meio da Nota Técnica nº 16/2022-CGGRIPE/DEIDT/SVS/MS, datada de 12 de novembro de 2022, foi emitido um alerta sobre o aumento no número de casos de COVID-19 e a circulação de novas linhagens da Variante de Preocupação (VOC) Ômicron, com ênfase nas sublinhagens BQ.1 e BA.5.3.1.

A Figura 4 mostra que a avaliação epidemiológica da COVID-19 no Brasil indicava a necessidade contínua de monitoramento epidemiológico do SARS-CoV-2 e suas variantes. Até 11 de novembro de 2022, foram registrados no país 34.908.198 casos e 688.656 óbitos acumulados de COVID- 19.

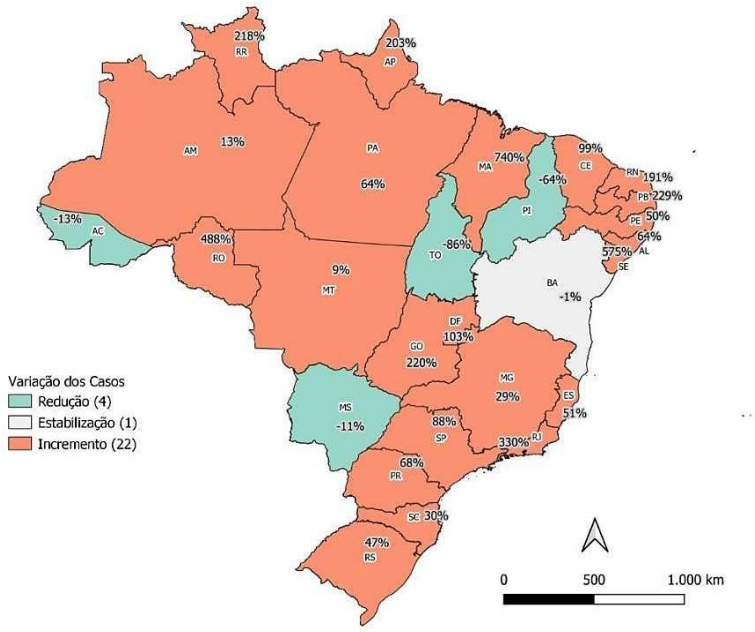
Figura 4. Situação do Brasil na SE 43(23 a 29 de outubro de 2022).



Fonte: https://covid19.who.int/region/amro/country/br.

Ao avaliar a variação percentual entre os casos novos de COVID-19 notificados na SE 45 comparados aos da SE 44, identificou-se que 21 unidades federativas apresentaram aumento (Figura 5), com destaque para Maranhão (740%), Sergipe (575%), Rondônia (488%), Rio de Janeiro (330%), Paraíba (229%), Goiás (220%), Roraima (218%), Amapá (203%),Rio Grande do Norte (199%) e Distrito Federal (103%).

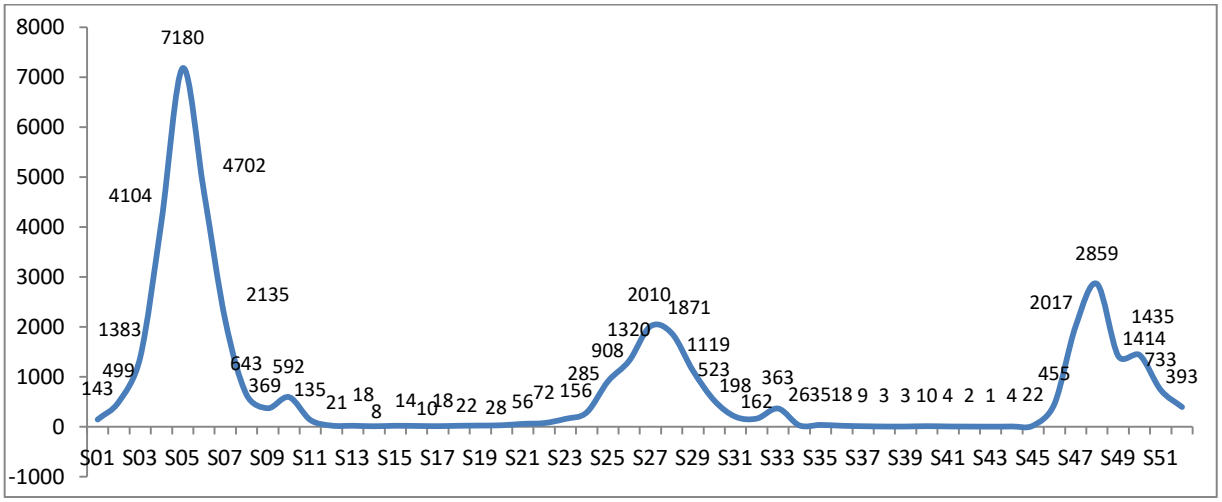
Figura 5. Distribuição espacial da variação de casos novos de COVID-19 por data de notificação da SE 45 comparada à SE 44. Brasil, 2022.



Fonte: Secretarias Estaduais de Saúde.

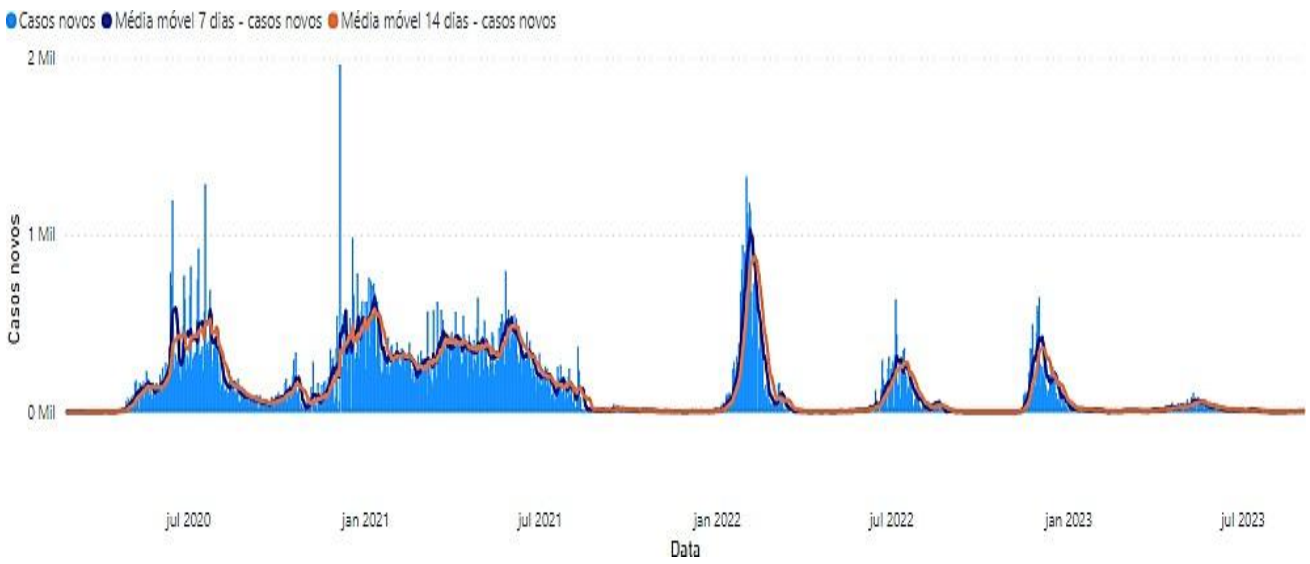
Em Aracaju, no ano de 2022, a variação percentual entre os novos casos de COVID-19 notificados na SE 45 em comparação com os da SE 44 mostrou um aumento de 450%, e em relação à SE 46 em comparação com a SE 45 (Figura 6), houve um aumento de 1968% nos casos novos. Esse período no município foi caracterizado pela ocorrência da quinta onda de COVID-19 em um intervalo de 3 anos (Figura 7).

Figura 6. Distribuição de casos novos por SE em Aracaju/SE, 2022.



Fonte: Sala de Situação – Secretaria Municipal de Saúde de Aracaju.

Figura 7. Distribuição de casos novos por dia, média móvel de 7 dias e média móvel de 14 dias, em Aracaju/SE, 2020-2023.



Fonte: Sala de Situação – Secretaria Municipal de Saúde de Aracaju.

3.3 Vacinas

Em meio à pandemia de COVID-19, o mundo e a comunidade científica uniram esforços para criar vacinas com o objetivo de mitigar os efeitos do vírus e restaurar uma certa normalidade na vida cotidiana, assemelhando-se às condições pré-pandemia. As vacinas surgiram como instrumentos vitais no controle da propagação do vírus.

A vacina ChAdOx nCoV-19, reconhecida através do nome dos seus criadores, a Universidade de Oxford e a AstraZeneca, é uma conquista notável no campo da biotecnologia. Esta vacina opera com base na tecnologia de vetor viral, onde um adenovírus, incapaz de se replicar, é utilizado para transportar material genético do SARS-CoV-2 para o organismo humano, induzindo assim uma resposta imune. No Brasil, a sua produção foi realizada em conjunto com a Fundação Oswaldo Cruz (Fiocruz). Após rigorosos ensaios clínicos em vários países, constatou-se que sua eficácia poderia ser potencializada com uma dose de reforço aplicada 28 dias após a primeira administração, garantindo uma resposta imunológica mais consistente (Knoll et al., 2021).

Alternativamente, a CoronaVac, criada pela Sinovac Life Sciences de Pequim, segue a tecnologia de vírus inativado. Esta vacina, administrada inicialmente em duas doses, utiliza o

SARS-CoV-2 inativado, um processo alcançado por meio de substâncias químicas como formaldeído. Este método tem sido central na produção da CoronaVac, facilitando uma resposta imune sem introduzir o vírus ativo no corpo. A vacina ganhou aprovação emergencial em 22 países, atestando sua eficiência e segurança (BUTANTAN, 2021; Tanriover et al., 2021).

A vacina Ad26.COV2.S, uma criação da Janssen, uma divisão da Johnson & Johnson, se destaca por sua tecnologia de vetor de adenovírus recombinante não replicante. Derivada de um isolado clínico inicial em Wuhan, China, esta vacina utiliza o adenovírus como meio de transportar o DNA que codifica uma porção do SARS-CoV-2, promovendo uma resposta imune robusta sem a replicação do vírus no organismo. A estratégia adotada demonstrou estimular uma imunidade potente contra o vírus (Sadoff et al., 2021).

Por fim, a colaboração entre a Pfizer e a BioNTech resultou na vacina BNT162b2, um imunizante que utiliza tecnologia mRNA encapsulado em nanopartículas lipídicas para codificar a proteína spike do SARS-CoV-2. Este mRNA, uma vez dentro das células humanas, direciona a síntese da proteína spike, incitando assim uma resposta imune potente e a produção de anticorpos neutralizantes. O esquema de vacinação preconizado envolve duas doses administradas com um intervalo de três semanas, proporcionando uma imunidade célula-mediada significativa contra o vírus (Oliver et al., 2020).

As vacinas têm mostrado ser uma barreira eficaz contra a COVID-19, oferecendo não apenas proteção individual, mas também contribuindo para a segurança da comunidade como um todo (Dhillon; Altmann; Male, 2021). A imunização promove uma resposta imunológica robusta, incluindo a geração de anticorpos que trabalham para neutralizar o vírus, reduzindo assim a possibilidade de infecção grave e transmissão subsequente do vírus. Ao proporcionar uma linha de defesa individual e coletiva contra o vírus, a vacinação se revela como a estratégia vital na contenção da pandemia, facilitando uma retomada gradual à normalidade e garantindo a proteção da população em geral (Wiysonge et el., 2022)

3.4 Eficácia das Vacinas

As vacinas contra a COVID-19, recomendadas pela OMS, demonstraram ser altamente eficazes na prevenção de formas graves da doença, bem como na redução de hospitalizações e mortes, atuando contra todas as variantes do vírus SARS-CoV-2, inclusive

as variantes Delta e Ômicron. Elas também têm demonstrado ser significativamente eficazes na diminuição da transmissão do vírus, mesmo que não consigam impedir completamente a infecção. A pesquisa continua, com a OMS mantendo uma estreita colaboração com pesquisadores e autoridades sanitárias para monitorar o impacto das variantes emergentes sobre a eficácia das vacinas (OPAS, 2023).

Evidências acumuladas destacam a eficácia notável das vacinas contra a COVID-19, incluindo CoronaVac, Pfizer/BioNTech e AstraZeneca, na mitigação de sintomas individuais graves da doença, o que se traduz em uma diminuição marcante nas hospitalizações, admissões em UTIs e mortes relacionadas à doença (Voysey et al., 2021). Uma revisão sistemática com meta-análise, publicada na revista *Infectious Diseases of Poverty* (Liu et al., 2021), quantificou a eficácia das vacinas em várias frentes, mostrando resultados promissores na prevenção de infecções (85%, IC 95%, 81-89%), COVID-19 sintomática (97%, IC 95%, 97-98%), internações hospitalares (93%, IC 95%, 89-96%), admissões em UTI (96%, IC 95%, 93-98%) e mortes (95%, IC 95%, 92-98%) relacionadas à doença. Além disso, o estudo ilustra uma incidência baixa de eventos adversos pós-vacinação.

Em relação à variante Ômicron, apesar de estudos demonstrarem a necessidade de doses de reforço em decorrência da redução na atividade neutralizante do vírus ao longo do tempo (Andrews et al., 2022), evidências recentes têm demonstrado que indivíduos vacinados mantêm a imunidade das células T a esta variante (Keeton et al., 2022), potencialmente equilibrando o declínio de anticorpos neutralizantes importantes na prevenção de casos mais graves da COVID-19.

Não se pode refutar os efeitos positivos da vacinação, incluindo aqui os referentes à terceira onda relacionada à disseminação fulminante da variante Ômicron no país. Com a cobertura vacinal em 73% à época, mesmo quando o país havia registrado cerca de 3,5 milhões de casos entre as semanas epidemiológicas 5 e 8 (de 30 de janeiro a 26 de fevereiro de 2022), foi percebida uma taxa de letalidade de apenas 0,6% relacionada à COVID-19. Considerando um cenário hipotético com baixa cobertura vacinal e taxa de letalidade variando de 2,7% a 4,3% como observado durante as duas primeiras ondas da pandemia, o Brasil poderia ter registrado um número de mortes 4 a 7 vezes maior que o confirmado (Martins-Filho et al., 2022b). Assim, percebemos que a cobertura vacinal alcançada no país tem se mostrado fundamental na prevenção de hospitalizações por casos graves e óbitos associados à doença (Han et al., 2021).

O impacto da vacinação na transmissão do vírus entre indivíduos vacinados também tem sido motivo de análise (Wienkes et al., 2022). Nesse estudo, foram avaliadas as características da infecção e transmissão pelo SARS-CoV-2 (variante Delta) entre indivíduos vacinados e não-vacinados a partir de um surto de COVID-19 identificado oito dias após a realização de um casamento nos Estados Unidos, apontando para o risco de um participante não-vacinado ser infectado pelo SARS-CoV-2 ter sido significativamente maior em comparação aos participantes do casamento totalmente vacinados (RR, 2.64; IC 95% 1.71-4.06; p = 0.001).

Além do estudo anteriormente relatado, outros trabalhos publicados em importantes revistas científicas de circulação mundial (Singanayagam et al., 2022) têm mostrado que as vacinas disponíveis não apenas protegem o vacinado e reduzem a carga viral, mas também oferecem proteção contra a transmissão do vírus para contatos próximos. Apesar das evidências emergentes demonstrarem que as vacinas disponíveis reduzem o risco de infecção pelo novo coronavírus e aceleram a eliminação viral, indivíduos completamente vacinados com infecções inesperadas podem apresentar pico de carga viral semelhante ao de indivíduos não-vacinados a partir de dois ou três meses após a vacinação (Levine-Tiefenbrun et al., 2021), e assim transmitir a infecção com eficiência em ambientes domésticos, onde a exposição é próxima e prolongada.

Cerqueira-Silva et al. (2022), analisando a efetividade da Coronavac entre individuos que foram previamente contaminados, demonstraram que as vacinas fornecem proteção a mais contra infecção sintomática e desfechos graves, como hospitalização e morte, em pessoas que já haviam sido infectadas com o novo coronavírus, criticando a ideia de imunidade de rebanhoem nível populacional por meio da infecção natural. A literatura aponta ainda que o impacto da vacinação em longo prazo na transmissibilidade do SARS-CoV-2 continua sendo mais bem estudado, de modo que qualquer argumento que invalide a importância da imunização pela administração de vacinas perde o sentido, à medida que expõe indivíduos à infecção e a desfechos clínicos deletérios associados à COVID-19.

No contexto global da pandemia, que resultou em mais de seis milhões de mortes, sendo mais de 10% concentradas no Brasil, a importância das estratégias de vacinação não pode ser subestimada. Negar a relevância da vacinação utilizando argumentos infundados que focam no caráter emergencial de sua aprovação é insustentável, dado o corpo substancial de

evidências que destaca a eficácia das vacinas na prevenção de desfechos desfavoráveis associados à COVID-19.

É fundamental reconhecer que a ciência é um processo dinâmico e acumulativo, adaptando-se e evoluindo com a emergência de novas evidências. As políticas públicas de saúde refletem essa natureza adaptável da ciência, como demonstrado pela recomendação do Ministério da Saúde para administração de uma segunda dose de reforço para idosos acima de 80 anos que receberam a primeira dose de reforço há mais de quatro meses.

3.5 A vacinação contra COVID-19 em Aracaju

A vacinação contra a COVID-19 em Aracaju iniciou-se em 19 de janeiro de 2021, mesmo período do inicio da vacinação no Brasil e no estado de Sergipe, alinhada às diretrizes do Plano Nacional de Operacionalização da Vacinação contra a COVID-19. Nessa primeira etapa, os grupos prioritários, incluindo profissionais de saúde, idosos e pessoas com comorbidades, foram os primeiros a receber as vacinas CoronaVac e Oxford/AstraZeneca. Gradualmente, à medida que mais doses se tornaram disponíveis, a campanha de vacinação foi ampliada para abranger outros grupos populacionais, como trabalhadores da educação, gestantes, puérperas e pessoas em situação de rua, aumentando progressivamente a faixa etária elegível.

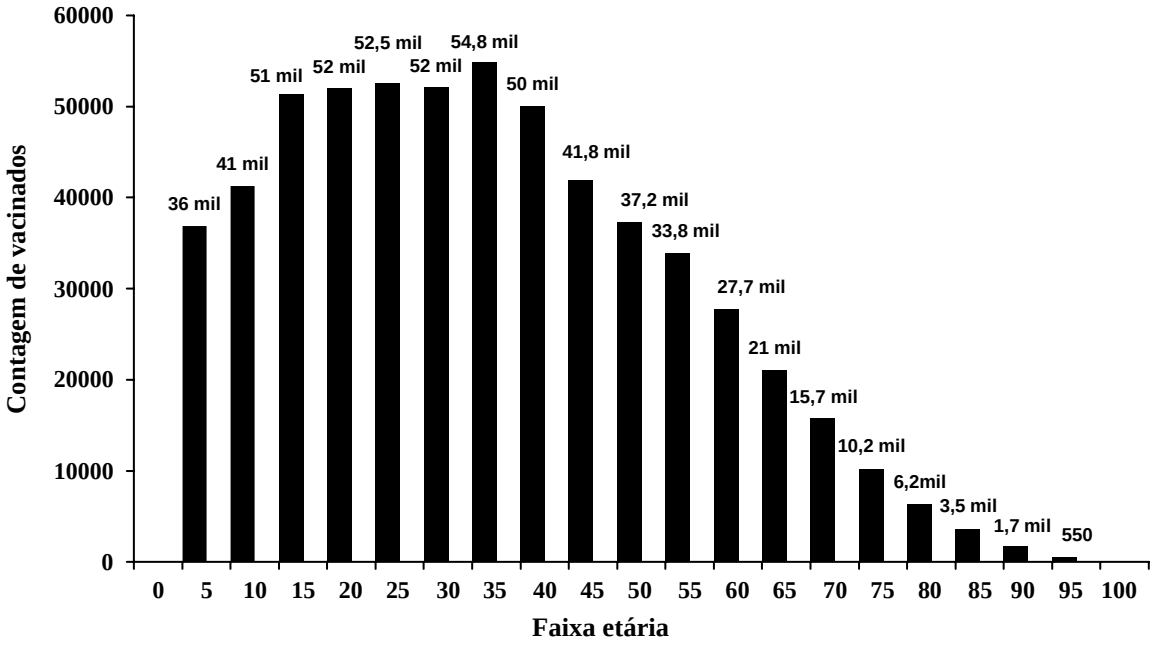
Para garantir o sucesso dessa grande operação, a Secretaria Municipal da Saúde de Aracaju desenvolveu um planejamento estratégico robusto. Estabeleceram-se metas, diretrizes e cronogramas, identificando os grupos prioritários de acordo com as recomendações do plano nacional. Vários pontos de vacinação foram configurados na cidade, abrangendo locais como postos de saúde, escolas e ginásios, para facilitar o acesso à vacinação para toda a população. Um aspecto fundamental do plano foi a implementação do sistema online Vacinaju, que auxiliava no agendamento e cadastramento para a vacinação. Esse sistema permitiu um fluxo mais organizado e evitou aglomerações nos pontos de vacinação. Simultaneamente, foram lançadas campanhas intensivas de comunicação, utilizando diversos canais de mídia para disseminar informações vitais sobre a vacinação.

Além dos pontos fixos, a prefeitura de Aracaju mobilizou equipes móveis para alcançar pessoas com acesso limitado a esses centros. Essas equipes atuavam em residências, instituições de longa permanência e abrigos, assegurando que ninguém deixasse de ser

vacinado. A iniciativa contou também com parcerias de instituições públicas e privadas, ampliando a capacidade de vacinação e apoiando a logística da campanha. Os profissionais de saúde desempenharam um papel crucial nesse processo, sendo devidamente treinados para administrar as vacinas corretamente, além de monitorar eventos adversos e registrar dados pertinentes. O envolvimento comunitário também foi incentivado, com líderes locais e influenciadores ajudando a promover a campanha de vacinação.

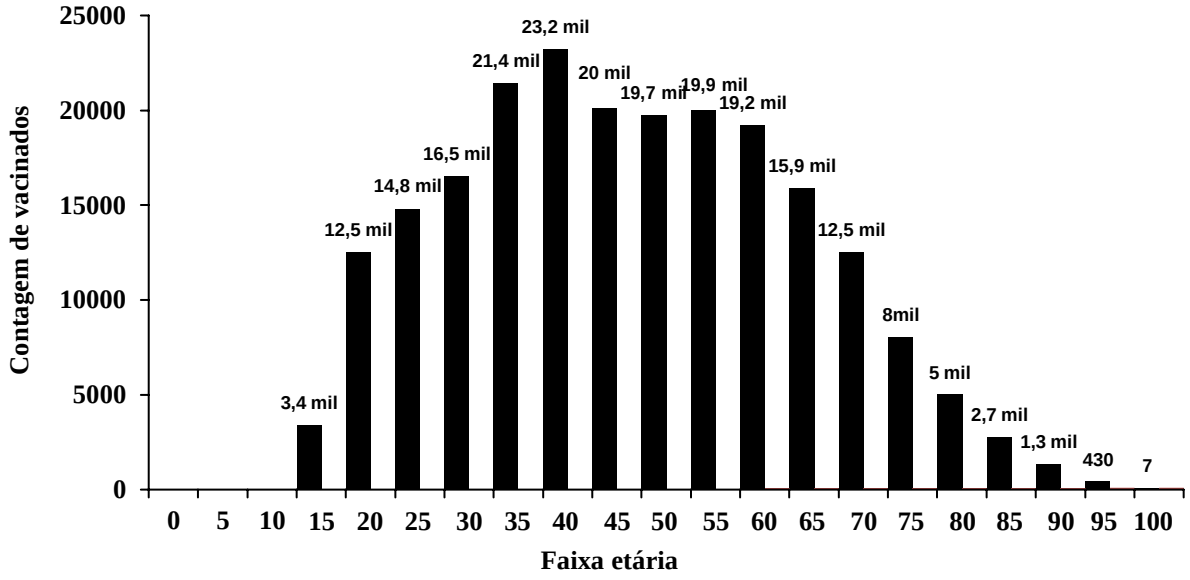
Ao chegar a 31 de dezembro de 2022, os esforços combinados resultaram em uma cobertura vacinal significativa em Aracaju. Naquele momento, 88,87% da população tinha recebido a primeira dose da vacina (Figura 8), enquanto 51,71% já estavam imunizados com a quarta dose (Figura 9).

Figura 8. Distribuição de vacinados com a primeira dose por faixa etária em Aracaju até o dia 31 de dezembro de 2022.



Fonte: IDS/PEC/Aracaju.

Figura 9. Distribuição de vacinados com a quarta dose por faixa etária em Aracaju até o dia 31 de dezembro de 2022.



Fonte: IDS/PEC/Aracaju.

4 MÉTODOS

4.1 Desenho do estudo

Trata-se de um estudo ecológico, onde a unidade de análise é uma população ou grupo de indivíduos, ao invés de um indivíduo específico. Nestes estudos, as medições são realizadas em um nível de grupo, que pode ser uma região geográfica, uma comunidade ou um período de tempo. Além disso, os estudos ecológicos permitem analisar dados já existentes para encontrar padrões, tendências e associações entre variáveis no nível da população.

4.2 Área de estudo

O estudo foi realizado em Aracaju, cidade portuária e capital do estado de Sergipe, no Nordeste do Brasil, reconhecida como a região mais pobre do país. Aracaju tem uma área de 182,2 km^2, uma população estimada em mais de 600.000 habitantes, e está dividida administrativamente em 42 bairros. Além disso, mais de um terço das famílias é de baixa renda e o Índice de Desenvolvimento Humano é de 0,770 (IBGE; www.ibge.gov).

O primeiro caso de COVID-19 na cidade de Aracaju foi confirmado em 14 de março de 2020 e 168.799 casos e 2.606 óbitos foram notificados até 31 de dezembro de 2022. As últimas 10 semanas epidemiológicas de 2022 (de 23 de outubro a 31 de dezembro) foram caracterizadas por um aumento repentino no número de casos da doença como resultado da transmissão comunitária da Ômicron BQ.1.1 e durante esta quinta onda de COVID-19, 9.349 casos e 14 mortes foram confirmados na cidade.

4.3 População de interesse

Este estudo incluiu todos os pacientes maiores de 18 anos, residentes em Aracaju, que tiveram COVID-19 confirmada por teste de reação em cadeia da polimerase (PCR), e foram internados em hospitais públicos e privados da cidade no período de 23 de outubro a 31 de dezembro de 2022. No período estudado só estava liberada pelo Ministério da Saúde a vacinação com 4 doses para o público maior de 18 anos (Nota Técnica Nº 114/2022-DEIDT/SVS/MS).

4.4 Coleta de dados

Este estudo incluiu todos os pacientes maiores de 18 anos residentes em Aracaju que tiveram COVID-19 confirmada por teste de reação em cadeia da polimerase (PCR) e foram internados em hospitais públicos e privados da cidade no período de 23 de outubro a 31 de dezembro de 2022. Os dados da COVID-19 foram extraídos do catálogo de microdados da Secretaria Municipal da Saúde de Aracaju e incluíram: (1) distribuição por sexo e idade; (2) condições clínicas pré-existentes associadas à gravidade da doença por COVID-19 (hipertensão, diabetes, doença pulmonar, doenças malignas, doença renal e doença cardíaca); (3) data de admissão hospitalar; (4) tipo de leito (clínico ou UTI); (5) situação vacinal (não vacinado, vacinado com apenas uma dose de vacina, vacinado com duas doses, vacinado com três doses e vacinado com quatro doses); (6) data da última dose recebida; e (7) intervalo de tempo entre a última dose e a internação. A taxa de hospitalização foi realizada pela divisão dos casos internados por COVID-19 pelo número de casos novos no período estudado multiplicado por 100.

4.5 Análise estatística

Os dados foram relatados de forma descritiva, e uma análise de interação entre a idade e o intervalo de tempo entre a última dose da vacina, a internação e o tipo de leito foi realizada por meio de uma análise de variância (ANOVA) de duas vias. Valores de $p < 0,05$ foram considerados estatisticamente significativos. As análises foram realizadas usando o software JASP versão 0.13 (JASP, Amsterdã, Holanda).

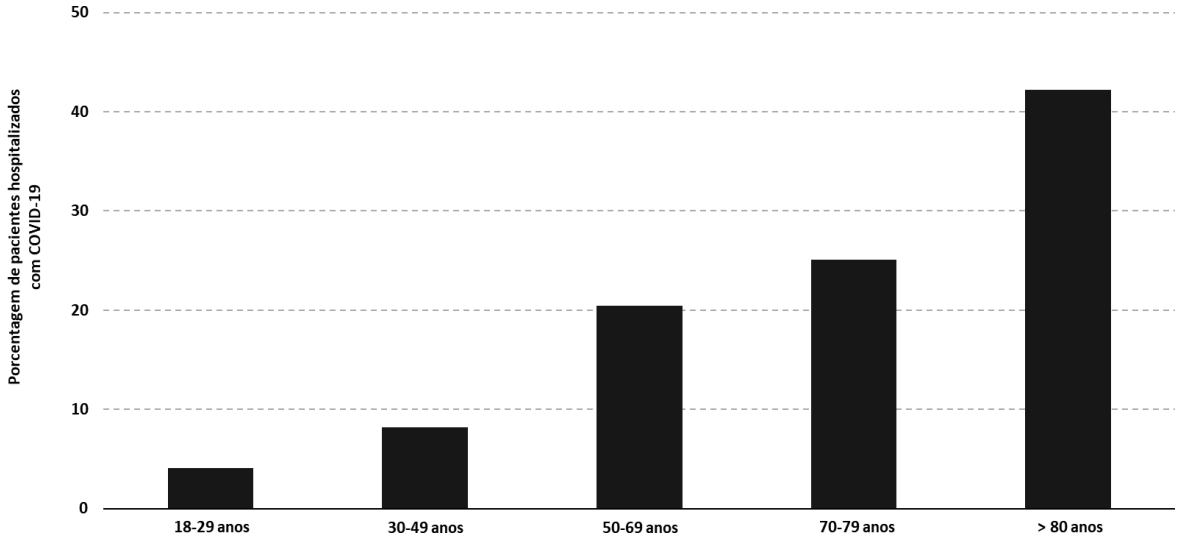
4.6 Aspectos éticos

A aprovação ética formal não foi necessária, pois todos os dados incluídos são dados secundários anônimos.

5 RESULTADOS

Um total de 147 adultos foram internados por COVID-19 no período de 23 de outubro a 31 de dezembro de 2022, sendo 78 (53%) do sexo feminino e 69 (47%) do sexo masculino, 105 (71,4%) com condições clínicas pré-existentes associadas à gravidade da COVID-19, destes 78 (74,3%) apresentando a hipertensão arterial sistêmica e outras condições como a comorbidade mais prevalente, destes 41(52,6%) tendo a diabetes mellitus em conjunto com a hipertensão arterial sistêmica. A mediana de idade foi de 77 anos (Q1 = 59; Q3 = 85), e aproximadamente 67% dos pacientes hospitalizados tinham mais de 70 anos de idade (Figura 10).

Figura 10. Porcentagem de pacientes hospitalizados por COVID-19 por idade.



Cento e dez (74,8%) pacientes foram admitidos em leitos hospitalares clínicos e 37 (25,2%) foram admitidos em UTI (Figura 11). Dos pacientes internados em leitos hospitalares clínicos 77 (70%) foram admitidos em hospitais privados e 33 (30%) em hospitais públicos, dos 37 (25,2%) pacientes admitidos em leitos de UTI, 32 (86,5%) foram admitidos em hospital privado e 5 (13,5%) em hospitais públicos. Durante o período do estudo, a taxa geral de hospitalização no município foi de 1,6%.

Figura 11. Distribuição do internamento por tipo de leito.

Variáveis	N (147)	Percentual
Tipo de Leito		
Clínico	110	74,8%
UTI	37	25,2%

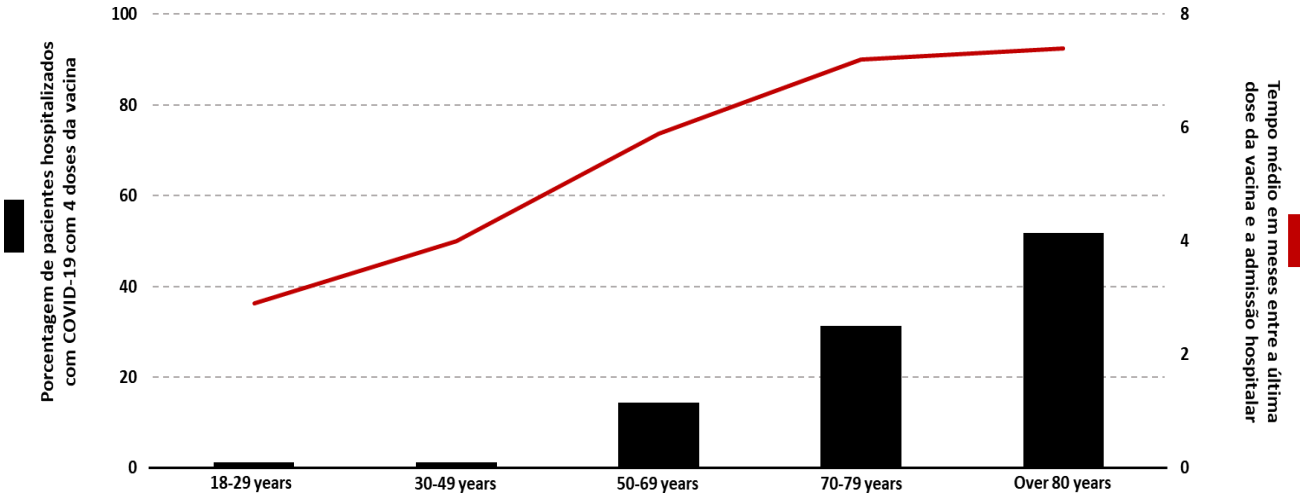
A Figura 12 mostra a distrinbuição do internamento em relação ao status vacinal para COVID-19, oito (5,5%) pacientes não foram vacinados; quatro (2,7%) pacientes receberam apenas uma dosede vacina; e 135 (91,8%) pacientes receberam o esquema primário contra COVID-19 com esquema de vacinação em duas doses. Entre os 135 que haviam sido vacinados com duas doses, 128 (94,8%) receberam um reforço (terceira dose) da vacina e 83 (61,5%) também receberam uma quarta dose.

Figura 12. Distribuição do internamento por condição vacinal.

Variáveis	**N**	**Percentual**
Vacinados (N 147)		
Nenhuma dose	8	5,5%
1 dose	4	2,7%
2 doses (esquema primário)	135	91,8%
Vacinados com reforço (N 135)		
3 dose	128	94,8%
4 dose	83	61,5%
Vacinados com 4 doses e idade (N 83)		
4 doses menor de 70 anos	14	17%
4 doses maior de 70 anos	69	83%
Ultima dose e internação hospitalar maior de 70 anos (N 69) *		
Menos de 6 meses	10	14,5%
Mais de 6 meses	59	85,5%

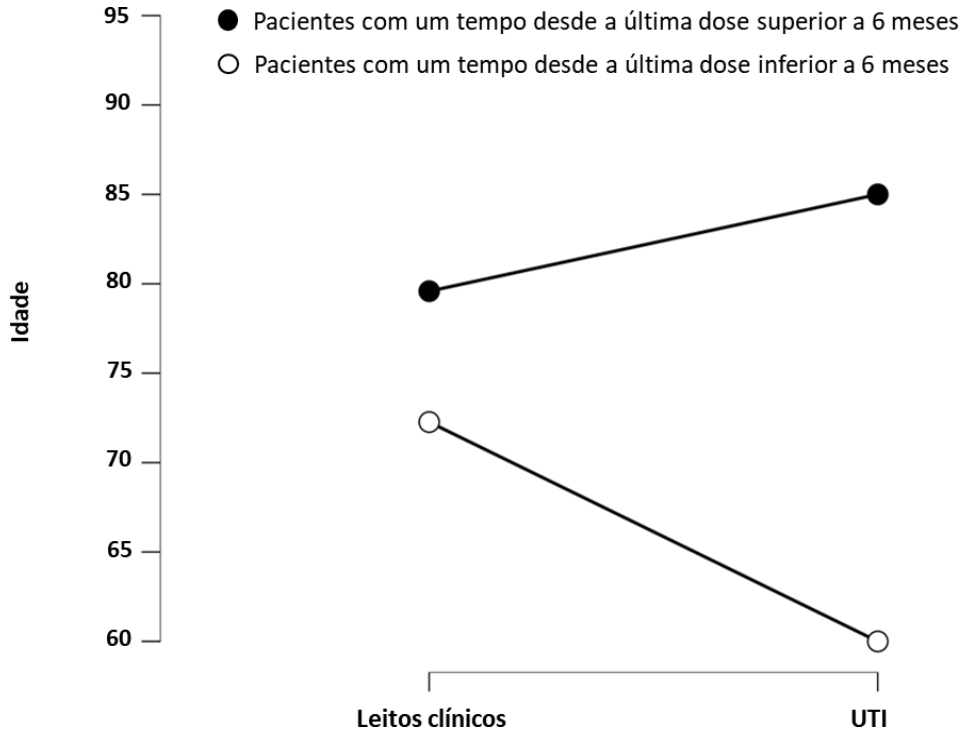
Aproximadamente 83% dos pacientes totalmente vacinados com quatro doses tinham 70 anos ou mais e pelo menos 75% receberam a última dose da vacina seis meses antes da internação hospitalar (mediana de 7,4 meses; Q1 = 6,2; Q3 = 8,0) (Figura 13).

Figura 13. Porcentagem de pacientes internados com COVID-19 que receberam a quarta dose da vacina e o tempo médio entre a última dose e a data de admissão.



Além disso, encontramos uma relação entre idade avançada, intervalo de tempo de pelo menos seis meses entre a última dose da vacina e a internação hospitalar e a necessidade de cuidados em UTI (p = 0,017) (Figura 14).

Figura 14. Análise de interação entre a idade, o intervalo de tempo entre a última dose da vacina e a internação, e o tipo de leito.



6 DISCUSSÃO

A análise conjunta dos resultados recentes e da literatura atual ilustra uma fase crítica na gestão da pandemia de COVID-19 no Brasil, marcada por uma dinâmica complexa e a emergência de novas subvariantes do vírus. Os esforços substanciais de vacinação, que alcançaram uma cobertura significativa de 80% da população com pelo menos duas doses da vacina, representam um marco crucial na tentativa de mitigar os efeitos da pandemia. No entanto, os surtos ressurgentes, especialmente aquele relacionado à variante Ômicron BQ.1.1, demonstram que estratégias mais adaptativas e nuanceadas são necessárias, particularmente no cenário brasileiro onde desigualdades sociais e desinformação se apresentam como desafios significativos (Castro-Nunes e Ribeiro, 2022).

Pesquisas atuais destacam que tanto a vacinação inicial quanto as doses de reforço têm se mostrado bastante eficazes na prevenção de complicações sérias decorrentes da COVID-19 a curto prazo (Muhsen et al., 2022). Em trabalhos anteriores, já havíamos notado uma queda significativa nas taxas de hospitalização na região analisada, correspondendo a um aumento na cobertura vacinal: de 6,9% no período de janeiro a junho de 2021, quando predominavam as variantes Gama e Zeta e a cobertura vacinal era de 12%, para 1,7% entre janeiro e fevereiro de 2022, época em que a variante Ômicron estava em alta e 73% da população havia sido vacinada (Martins-Filho et al., 2022c). Este estudo corrobora a eficácia sustentada da campanha de vacinação, mostrando taxas de hospitalização semelhantes às do início de 2022, o que ressalta a importância de continuar com a vacinação, especialmente com o surgimento de novas subvariantes do Ômicron.

Apesar da eficácia demonstrada das vacinas na prevenção de casos graves e hospitalizações, as evidências também indicam uma diminuição da resposta imunológica ao longo do tempo, tanto após a infecção quanto após a vacinação completa (Rodriguez et al., 2022).

Uma revisão sistemática com análise de metarregressão mostrou uma redução na eficácia da vacina de 32,0 e 9,5 pontos percentuais para doença sintomática e grave por COVID-19, respectivamente, em idosos seis meses após a vacinação (Feikin et al., 2022). Além disso, há evidências de perda de anticorpos e redução da eficácia da vacina nos

primeiros seis meses após as doses de reforço. Um estudo realizado entre residentes de cuidados de longa duração com idade ≥ 60 anos em Ontário, Canadá, descobriu que a quarta dose proporcionou proteção adicional contra resultados relacionados com a Ômicron, mas a proteção diminuiu ao longo do tempo. Os autores sugeriram um reforço adicional 4–6 meses após o recebimento da quarta dose para continuar a fornecer maior proteção contra a infecção por SARS-CoV-2 para esta população vulnerável (Grewal et al., 2022).

Este estudo ecológico, junto com as tendências observadas em outros estudos, destaca uma preocupação crescente com a proteção de grupos etários mais avançados. A maioria dos hospitalizados tinha mais de 70 anos, um grupo que parece estar em maior risco de hospitalização e necessidade de cuidados intensivos, especialmente se o intervalo desde a última dose da vacina exceder seis meses. Assim, sinaliza uma urgente necessidade de revisão e possivelmente intensificação dos regimes de vacinação, incluindo a consideração de uma quinta dose para otimizar a proteção nesta demografia.

Além de ajustes nos esquemas de vacinação, uma resposta eficaz à pandemia deve abordar as disparidades sociodemográficas que podem influenciar a eficácia das intervenções de saúde pública. Iniciativas governamentais são necessárias para combater a desinformação e os movimentos antivacina, além de promover a equidade no acesso às vacinas através de políticas inclusivas e direcionadas (Martins-Filho et al., 2023).

O atual estudo também sublinha a necessidade de pesquisas adicionais para uma análise mais detalhada da imunogenicidade a longo prazo das vacinas contra COVID-19, com foco na produção e duração dos anticorpos neutralizantes. Este direcionamento de pesquisa pode fornecer *insights* críticos para desenvolver estratégias de vacinação mais sofisticadas e produzir políticas públicas mais eficazes.

7 CONCLUSÃO

Os achados deste estudo mostraram que os idosos com mais de 70 anos foram as pessoas que mais ficaram hospitalizadas no período da onda Ômicron BQ1.1 em Aracaju/SE, de 23 de outubro a 31 de dezembro de 2022, apresentaram necessidade de cuidados em leitos de UTI e 75% destes já tinha um intervalo de tempo superior há 6 meses da última dose da vacina contra COVID-19 e a data do internamento. Os achados sugerem que a quarta dose da vacina COVID-19 tem um efeito protetor de curto prazo na prevenção de casos mais graves da doença. Portanto, a situação vacinal dos pacientes hospitalizados com COVID-19 durante a onda Ômicron BQ.1.1 em Aracaju sugeriu a necessidade de políticas públicas para completaro esquema vacinal com quatro doses na população adulta. Apesar das limitações deste estudo, incluindo o pequeno tamanho da amostra e a falta de dados longitudinais de títulos de anticorpos neutralizantes, nossos achados também puderam sugerir a necessidade de uma quinta dose entre aqueles com mais de 70 anos, com tempo desde a última dose de mais de 6 meses.

Em conclusão, nossos achados destacam que o combate à COVID-19 no Brasil é uma batalha multifacetada que necessita de uma abordagem integrada e adaptativa, que leve em conta a evolução dinâmica do SARS-CoV-2. O desenvolvimento continuado de estratégias de saúde pública que respondam dinamicamente às descobertas emergentes é imperativo para garantir a máxima eficácia na contenção desta pandemia global.

8 CONSIDERAÇÕES FINAIS

Até 11 de dezembro de 2022, o município de Aracaju seguia as orientações do Ministério da Saúde, conforme a Nota Técnica Nº 221/2022-CGPNI/DEIDT/SVS/MS, que estabelecia diretrizes sobre o esquema primário e doses de reforço das vacinas contra a COVID-19 em pessoas imunocomprometidas. Essa nota técnica recomendava a administração da quinta dose da vacina em indivíduos com imunossupressão grave.

A inclusão da vacina contra a COVID-19 no calendário vacinal é uma medida que deve ser adotada em resposta à pandemia, várias são as razões que justificam essa inclusão: a proteção individual e coletiva, o controle da pandemia, a proteção de grupos de risco, a eficácia comprovada e, a adaptação a novas variantes. Incluir a vacina no calendário permite a administração de doses de reforço conforme necessário.

No entanto, a decisão de incluir a vacina contra a COVID-19 no calendário vacinal pode variar de acordo com as diretrizes de saúde pública de cada país e a disponibilidade das vacinas. É importante que as decisões sejam baseadas em evidências científicas e na orientação de especialistas em saúde. A vacinação em massa é uma ferramenta crucial para superar a pandemia e proteger a saúde pública.

Após análise desse estudo, a Secretaria Municipal de Saúde de Aracaju, em 12 de dezembro de 2022, decidiu instituir a aplicação da quinta dose em pessoas com mais de 70 anos que já haviam recebido a quarta dose há mais de seis meses. Essa medida teve como objetivo principal conter o rápido aumento de casos graves e óbitos relacionados à COVID-19 na cidade durante a onda da variante Ômicron BQ.1.1.

Essas ações e decisões tomadas pela autoridade de saúde no nível municipal reflete o compromisso em proteger a população contra os efeitos adversos da COVID-19 e garantir a continuidade dos esforços de imunização em Aracaju.

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APÊNDICE A

ARTIGO PUBLICADO NA EXCLI JOURNAL – EXPERIMENTAL AND CLINICAL SCIENCES

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Letter to the editor:

THE VACCINATION STATUS OF COVID-19 HOSPITALIZED PATIENTS DURING THE OMICRON BQ.1.1 WAVE IN NORTHEAST BRAZIL SUGGESTS THE NEED FOR A FIFTH BOOSTER DOSE IN THE ELDERLY, WITH A TIME SINCE THE LAST DOSE OF MORE THAN 6 MONTHS

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Vaccines against COVID-19 have been shown to be the most effective, safe, and cost-effective measure in preventing hospitalizations, admissions to intensive care units (ICU), and deaths from the disease. Despite studies demonstrating that vaccinated individuals maintain T cell immunity to SARS-CoV-2 (Keeton et al., 2022), it has been suggested that the virus's neutralizing activity declines over time and the need for booster doses especially against Omicron subvariants (Renia et al., 2022). Furthermore, real-world studies have revealed evidence of waning vaccine effectiveness in a few months following the third (Goh et al., 2022) and fourth doses (Nordström et al., 2022), as well as the possibility of at least one COVID-19 wave recurrence in the range 3-9 months (Cappi et al., 2022), eliciting debate on the need for additional doses at regular intervals.

Although 80 % of the Brazilian population is immunized against COVID-19 with two doses of CoronaVac (Sinovac/Butantan), Covishield (Oxford-AstraZeneca/Fiocruz), or ComiRNAty (Pfizer/BioNTech) vaccines, or a single-dose J&J/Janssen vaccine, and at least 50 % having received a booster dose, a fifth wave of COVID-19 associated with the Omicron BQ.1.1 circulation has occurred in the country at the end of 2022, increasing the number of hospitalizations and deaths from the disease. In this retrospective cohort study, we evaluated the vaccination status among COVID-19 hospitalized patients during the Omicron BQ.1.1 wave in Brazil. The study was conducted in Aracaju, a port city and the capital of Sergipe state in the Northeast Brazil, recognized as the poorest region in the country.

Aracaju has an area of 182.2 km^2, an estimated population at over 600 000 inhabitants, and is divided administratively into 42 neighborhoods. In addition, more than one-third of families are low-income, and the Human Development Index is 0.770 (Brazilian Institute for Geography and Statistics; www.ibge.gov). The first case of COVID-19 in the city was confirmed on March

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14, 2020, and 168 799 cases and 2606 deaths were reported until December 31, 2022. The last 10 epidemiological weeks of 2022 (from October 23 to December 31) were characterized by a sudden increase in the number of disease cases as a result of community transmission of the Omicron BQ.1.1, and during this fifth wave of COVID-19, 9332 cases and 14 deaths were confirmed in the city. In Aracaju, the COVID-19 vaccination campaign started on January 19, 2021. As of December 31, 2022, general population vaccination coverage was approximately 83 %, with 67 % having received at least one booster dose (https://todoscontraocorona.net.br/; https://transparencia.aracaju.se.gov.br/prefeitura/covid19/).

This study included all patients over the age of 18 living in Aracaju who had COVID-19 confirmed by polymerase chain reaction testing and were admitted to public and private hospitals in the city from October 23 to December 31, 2022. Data on COVID-19 were extracted from the microdata catalog of the Aracaju Municipal Health Department and included: (1) sex and age distribution; (2) pre-existing clinical conditions associated with COVID-19 disease severity (hypertension, diabetes, lung disease, malignancies, kidney disease, and heart disease); (3) date of hospital admission; (4) bed type (clinical bed or ICU); (5) vaccination status (unvaccinated, vaccinated with only one dose of vaccine, vaccinated with two doses, vaccinated with three doses, and vaccinated with four doses); (6) date of last dose received; and (7) time interval between the last dose and hospital admission. Data were reported descriptively, and an interaction analysis between age, the time interval between the last vaccine dose and hospital admission, and bed type was performed using a two-way analysis of variance (ANOVA). P-values < 0.05 were considered statistically significant. Analyses were performed using JASP software version 0.13 (JASP, Amsterdam, the Netherlands). Formal ethical approval is not required as all data included are anonymous secondary data.

From October 23 to December 31, 2022, 147 adults were hospitalized due to COVID-19, with 69 (47 %) being male and 105 (71.4 %) having pre-existing clinical conditions associated with the COVID-19 disease severity. The median age was 77 years (Q1 = 59; Q3 = 85), and approximately 67 % of hospitalized patients were over 70 years of age (Supplementary Figure 1). A total of 110 (74.8 %) patients were admitted to clinical hospital beds and 37 (25.2 %) were admitted to an ICU. During the study period, the overall hospitalization rate was 1.6 %. Regarding COVID-19 vaccine status, eight (5.4 %) patients were unvaccinated; four (2.7 %) patients had only received one dose of vaccine; and 135 (91.8 %) patients had received the primary schedule against COVID-19 with a two-dose vaccination regimen. Among those who had vaccinated with two doses, 128 (94.8 %) had received a booster (third dose) of the COVID-19 vaccine; 83 (64.8 %) had also received a fourth dose. Approximately 83 % of fully vaccinated patients with four doses were aged 70 years or older, and at least 75 % had their last dose of the COVID-19 vaccine 6 months before hospital admission (median 7.4 months; Q1 = 6.2; Q3 = 8.0) (Supplementary Figure 2). Furthermore, we found a relationship between advanced age, a time interval of at least 6 months between the last vaccine dose and hospital admission, and the need for ICU care ($p = 0.017$) (Supplementary Figure 3).

Consistent evidence in the literature shows that the primary COVID-19 vaccine cycle and booster doses are effective in preventing COVID-19-related outcomes in the short-term (Muhsen et al., 2022). Previously, we demonstrated a decrease in hospitalization rates in this region as vaccination coverage increased, ranging from 6.9 % during the predominance of the Gamma and Zeta variants (January - June 2021; vaccination coverage: 12 %) to 1.7 % during the wave associated with the Omicron variant (January - February 2022; vaccination coverage: 73 %) (Martins-Filho et al., 2022). The current study showed a hospitalization rate comparable to that observed in early 2022, emphasizing the importance of the COVID-19 vaccination campaign as new Omicron subvariants emerge.

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However, studies have found a progressive decline in the humoral response to SARS-CoV-2 during the first 6 months after infection (de Lima Silva et al., 2022) or after being fully vaccinated (Rodriguez et al., 2022). A systematic review with meta-regression analysis showed a reduction in vaccine effectiveness of 32.0 and 9.5 percentage points for symptomatic and severe COVID-19 disease, respectively, in older people 6 months after vaccination (Feikin et al., 2022). Furthermore, there is evidence of loss of antibodies and reduced vaccine effectiveness in the first 6 months after the booster doses. A test-negative study (Grewal et al., 2022) conducted among long-term care residents aged ≥ 60 years in Ontario, Canada, found that the fourth dose provided additional protection against Omicron-related outcomes, but the protection waned over time. The authors suggested an additional booster 4–6 months after fourth dose receipt to continue to provide increased protection against SARS-CoV-2 infection for this vulnerable population.

Almost 70 % of hospitalized patients in the current study were over 70 years old, and slightly more than half had received four doses of the vaccine. Furthermore, among those fully vaccinated with all four doses, we found a greater need for ICU care when the interval between the last dose and the date of admission was longer than 6 months. These findings suggest that the fourth dose of COVID-19 vaccine has a short-term protective effect in preventing more severe disease cases. Therefore, the vaccination status of COVID-19 hospitalized patients during the Omicron BQ.1.1 wave in Northeast Brazil suggests the need of public policies to complete the vaccination schedule with four doses in the adult population. Despite the limitations of this study, including the small sample size and the lack of longitudinal data of neutralizing antibody titers, our findings may also suggest the need for a fifth dose among those over 70 years, with a time since the last dose of more than 6 months.

Authors' contributions

All authors contributed equally to this work.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Letter to the editor:

THE VACCINATION STATUS OF COVID-19 HOSPITALIZED PATIENTS DURING THE OMICRON BQ.1.1 WAVE IN NORTHEAST BRAZIL SUGGESTS THE NEED FOR A FIFTH BOOSTER DOSE IN THE ELDERLY, WITH A TIME SINCE THE LAST DOSE OF MORE THAN 6 MONTHS

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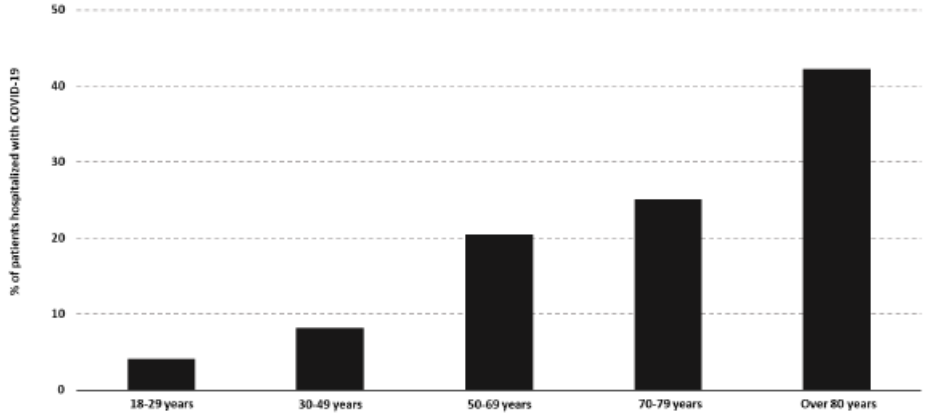
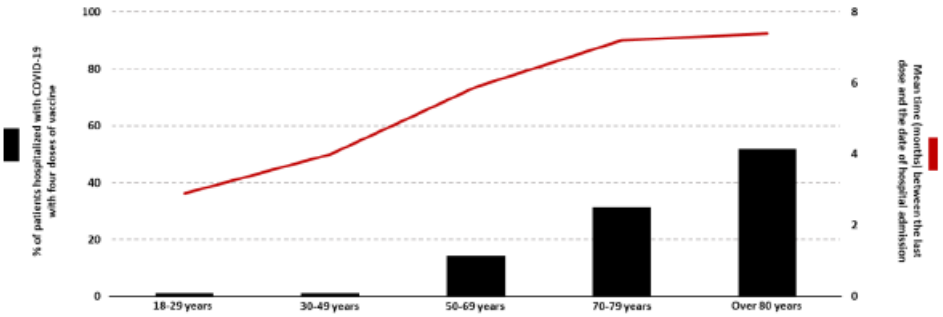


Supplementary Figure 1: Percentage of COVID-19 hospitalized patients according to age



Supplementary Figure 2: Percentage of patients hospitalized with COVID-19 who received the fourth dose of the vaccine and the mean time between the last dose and the date of admission

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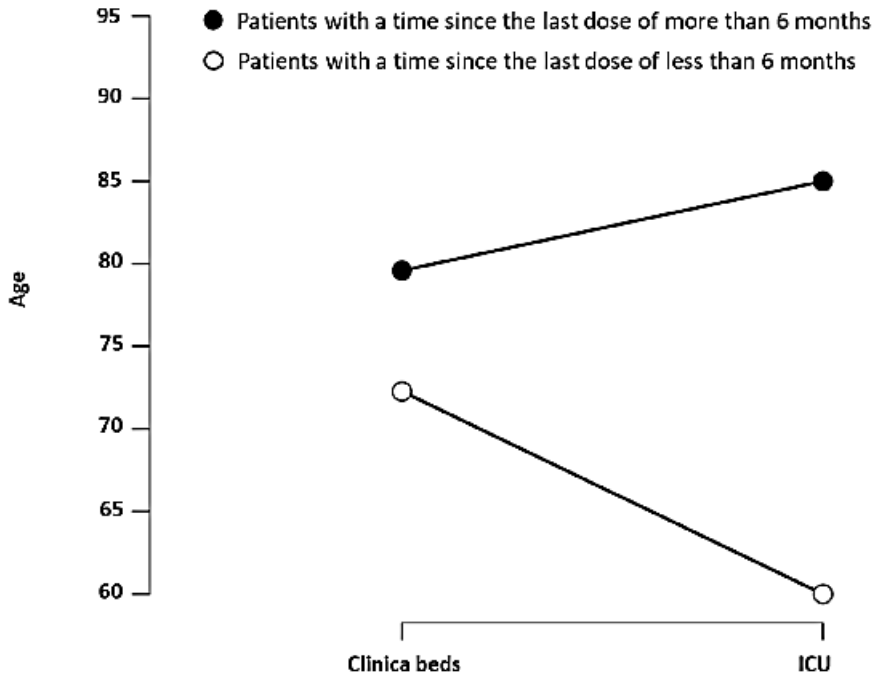

Supplementary Figure 3: Interaction analysis between age, the time interval between the last vaccine dose and hospital admission, and bed type

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BRIEF COMMUNICATION

Prevalence of SARS-CoV-2 infection among urban cleaning and solid waste management workers during transmission of the Omicron variant in Brazil

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This study estimated the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in urban cleaning and solid waste management workers during the transmission of the Omicron variant in one of the poorest regions of Brazil (the state of Sergipe). Nasopharyngeal swabs were collected from 494 workers, and the presence of SARS-CoV-2 RNA was tested by quantitative reverse-transcriptase polymerase chain reaction. Data on socio-demographic characteristics, comorbidities, vaccination status, mask use, and use of public transport to commute to the workplace were collected. The prevalence with a 95% confidence interval (CI) was calculated from the proportion of SARS-CoV-2 positive cases among the total number of individuals tested. The prevalence ratio (PR) with a 95% CI was the measure of association used to evaluate the relationship between SARS-CoV-2 infection and the exposure variables. The prevalence of SARS-CoV-2 infection was 22.5% (95% CI, 19.0 to 26.4). Individuals under the age of 40 had a higher prevalence of infection (PR, 1.53; 95% CI, 1.03 to 2.30) as well as those who did not believe in the protective effect of vaccines (PR, 1.78; 95% CI, 1.05 to 2.89). Our results indicate the need for better guidance on preventive measures against coronavirus disease 2019 among urban cleaning and solid waste management workers.

KEY WORDS: COVID-19, SARS-CoV-2, Waste management, Sanitation

INTRODUCTION

Urban cleaning and solid waste management workers play a vital role in communities by collecting accumulated solid waste and recycling items from residential areas, commercial centers, industrial companies, and public parks. In Brazil, more than 370,000 people work in this activity and collect 135,000 tons of garbage per day, including domestic and public waste. Most of these workers have low education and earn just over US$300 per month [1].

In the coronavirus disease 2019 (COVID-19) pandemic, waste collectors have been one of the highest occupational risk groups for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, along with healthcare professionals [2]. Under experimental conditions, SARS-CoV-2 has been shown to remain viable for up to 72 hours on plastic, stainless steel, copper, and cardboard [3]. COVID-19 patients undergoing home treatment may dispose of infectious household waste, which can pose a risk to workers and the environment [4]. Concerns have been raised regarding the disposal of contaminated face masks as general waste. In ad-

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dition, waste management is an essential service and has operated continuously during the pandemic, even in areas categorized as high risk for COVID-19.

However, studies evaluating the exposure of urban cleaning and solid waste management workers to COVID-19 are rare. The present study estimated the prevalence of SARS-CoV-2 infection in this population during the transmission of the Omicron variant in one of the poorest regions of Brazil.

MATERIALS AND METHODS

Study design and context

This was a cross-sectional study carried out in Aracaju, a city in the state of Sergipe in Northeast Brazil, from February 1, 2022 to February 8, 2022, and included urban cleaning and solid waste management workers who worked in the city. Aracaju is a port city and the state capital of Sergipe, with an area of 182.2 km^2 and an estimated population of over 600,000 inhabitants. Furthermore, more than one-third of families are low-income, and the Human Development Index is 0.770.

Data collection and biological sample

Data and biological materials were collected from urban cleaning and solid waste management workers at the headquarters of the company responsible for waste collection in the city. Testing was voluntary and free of charge and was performed in collaboration with the Municipal Health Department of Aracaju. Workers who took the test provided information on their socio-demographic characteristics, the presence of comorbidities, vaccination status, mask use, and use of public transport to commute to the workplace. There was no restriction regarding age. During the collection period, trained assistants collected nasopharyngeal swabs bilaterally to perform tests using the quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) technique.

RNA isolation

The assay was performed according to the manufacturer's instructions by first extracting a 400-μL aliquot of the specimen into a commercial universal transport medium using the MagMAX Viral/Pathogen Nucleic Acid Isolation Kit and the KingFisher Flex Purification system (Thermo Fisher Scientific, Waltham, MA, USA). In addition, 10 μL of MS2 phage control was added to all specimens and to the negative control, which was used as an internal process control. The nucleic acid was eluted in 50 μL of elution solution.

Reverse-transcriptase polymerase chain reaction

SARS-CoV-2 was detected with 5 μL of extracted RNA using the TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermo Fisher Scientific), which has both a sensitivity and specificity of 100% (https://www.thermofisher.com/document-connect/document-connect.html?url=https%3A%2F%2Fassets.thermofisher.com%2FTFS-Assets%2FGSD%2FReference-Materials%2Ftaqpath-ceivd-rt-pcr-kit-technical-bulletin.pdf). The assay targeted 3 gene sequences (N2, ORF1ab, and S genes) and MS2, and was performed according to the manufacturer's instructions (https://assets.thermofisher.com/TFS-Assets/LSG/manuals/MAN0019215_TaqPath-COVID-19_CE-IVD_RT-PCR%20Kit_IFU.pdf). In brief, for each specimen, a master mix was prepared that contained TaqPath 1-Step Multiplex Master Mix (No ROX) COVID-19 real-time PCR assay multiplex, and nuclease-free water. Each run also included a SARS-CoV-2 positive control and a negative control. RT-qPCR analysis was performed on a QuantStudio 5 Real-Time PCR system (Thermo Fisher Scientific).

Statistical analysis

The outcome of interest was the prevalence of SARS-CoV-2 infection among urban cleaning and solid waste management workers. The point prevalence with a 95% confidence interval (CI) [5] was calculated from the proportion of SARS-CoV-2 positive cases diagnosed through RT-qPCR in the total number of individuals tested. The prevalence ratio (PR) with a 95% CI was the measure of association used to evaluate the relationship between SARS-CoV-2 infection and the exposure variables (sex [male and female], age [up to 39 and ≥40 years], use of public transport [yes or no] , frequency of use of public transport [1-2, 3-4, ≥5 times/wk], complete vaccination schedule [yes or no], and confidence in the protective effect of vaccines [yes, no or no response]). Statistical analyses were performed using the "epitools" package (https://cran.r-project.org/web/packages/epitools/index.html) in R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

This study is part of the EpiSERGIPE Project, which was approved by the Ethics Committee of the Federal University of Sergipe (protocol 33095120.4.0000.5546).

RESULTS

From a total of 852 urban cleaning and solid waste management workers, 494 were included in the present study, of whom 399 (80.8%) were male and 95 (19.2%) were female. The mean age was 39.1 years (standard deviation: 11.7 years). In total, 431 (87.2%) individuals reported no pre-existing medical conditions, and 57 (11.5%) reported the presence of hypertension or diabetes. Most workers (n=416, 84.2%) reported using public transport, with 58 (13.9%) using it 1-2 times/wk, 35 (8.4%) 3-4 times/wk, and 310 (74.5%) more than 5 times/wk. Thirteen workers did not report how frequently they used public transportation. Only 4 (0.8%) individuals reported not wearing a face mask.

Regarding vaccination status, 489 (99%) workers reported having received the first dose of COVID-19 vaccine (344 [70.3%] Pfizer-BioNTech; 56 [11.5%] Oxford-AstraZeneca; 45 [9.2%] CoronaVac; 2 [0.4%] Janssen; and 42 [8.6%] without information on the type of vaccine). Among the vaccinated individuals, 145 (29.7%) had a complete vaccination schedule and 344 (70.3%) were par-

tially vaccinated. Among subjects who received the first dose of the Pfizer-BioNTech vaccine, 115 (33.4%) were fully vaccinated at the time of data collection. For the Oxford-AstraZeneca and CoronaVac vaccines, the complete vaccination frequency was 23.2% (13 of 56) and 26.7% (12 of 45), respectively; 2 individuals were immunized with the Janssen vaccine; and in 3 situations, there was no record of the vaccine used. Fifty-six (11.3%) of the total workers included in the study stated that they did not believe in the protective effect of vaccines, 403 (81.6%) responded positively, and 35 (7.1%) did not respond; only 8 (14.3%) of those who responded negatively about vaccine confidence were fully vaccinated against COVID-19.

Table 1. Prevalence of SARS-CoV-2 infection among urban cleaning and solid waste management workers during community transmission of the Omicron variant in Northeast Brazil in 2022

Variables	RT-qPCR positive/ total, n (%)	Prevalence ratio (95% CI)	p-value
Sex			
Male	82/399 (20.6)	1.00 (reference)	
Female	29/95 (30.5)	1.50 (0.94, 2.30)	0.075
Age (yr)			
≤39	68/251 (27.1)	1.53 (1.03, 2.30)	0.028
≥40	43/243 (17.7)	1.00 (reference)	
Use of public transport			
No	16/78 (20.5)	1.00 (reference)	
Yes	95/416 (22.8)	1.11 (0.65, 2.03)	0.712
Frequency of use of public transport (times/wk)[1]			
1-2	15/58 (25.9)	1.00 (reference)	
3-4	8/35 (22.9)	0.88 (0.33, 2.22)	0.795
≥5	71/310 (22.9)	0.89 (0.50, 1.67)	0.653
COVID-19 vaccine - first dose[2]			
Oxford-AstraZeneca	10/56 (17.9)	1.00 (reference)	
Pfizer-BioNTech	77/344 (22.4)	1.25 (0.65, 2.72)	0.519
CoronaVac	12/45 (26.7)	1.49 (0.59, 3.86)	0.356
COVID-19 vaccine - second dose[3]			
Oxford-AstraZeneca	2/13 (15.4)	1.00 (reference)	
Pfizer-BioNTech	25/115 (21.7)	1.41 (0.35, 12.31)	0.699
CoronaVac	3/12 (25.0)	1.63 (0.19, 19.46)	0.626
Vaccination schedule			
Fully vaccinated	31/145 (21.4)	1.00 (reference)	
Not vaccinated[4] or partially vaccinated	80/349 (22.9)	1.07 (0.70, 1.68)	0.753
Confidence in the protective effect of vaccines			
Yes	85/403 (21.2)	1.00 (reference)	
Preferred not to answer	5/35 (14.3)	0.68 (0.21, 1.64)	0.411
No	21/56 (37.5)	1.78 (1.05, 2.89)	0.025

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-qPCR, quantitative reverse-transcriptase polymerase chain reaction; COVID-19, coronavirus disease 2019; CI, confidence interval.
[1]Thirteen individuals did not report the frequency of using public transport.
[2]Two subjects received the Janssen vaccine, and 42 subjects had no information about the vaccine received as a first dose.
[3]Three individuals had no information about the vaccine received.
[4]Only 5 individuals were not vaccinated, of whom 1 tested positive for COVID-19.

Of the 494 urban cleaning and solid waste management workers evaluated, 111 (22.5%; 95% CI, 19.0 to 26.4) were positive for the presence of SARS-CoV-2 according to the RT-qPCR test, and all were asymptomatic at the time of collection of data and biological material. Individuals under the age of 40 had a higher prevalence of infection (PR, 1.53; 95% CI, 1.03 to 2.30), as did those who did not believe in the protective effect of vaccines (PR, 1.78; 95% CI, 1.05 to 2.89). There was no difference in the prevalence of SARS-CoV-2 infection based on the frequency of use of public transportation. Of the 111 positive cases of SARS-CoV-2 infection, 80 occurred among unvaccinated or partially vaccinated workers, and 31 among those fully vaccinated. However, no differences were observed in the prevalence of infection according to the type of vaccine used or the workers' vaccination status (Table 1).

DISCUSSION

The first case of COVID-19 in Aracaju was identified on March 14, 2020, and as of March 12, 2022, 150,007 cases and 2,524 deaths associated with COVID-19 had been confirmed. The first 10 weeks of 2022 (January 2 to March 12) were characterized by a sudden increase in the number of cases as a result of community transmission of the Omicron variant, and during this third wave of COVID-19, 21,607 cases and 89 deaths were recorded in the city. COVID-19 vaccination coverage for the general population was 76.8% as of March 12, 2022.

The present study showed that one-fourth of urban cleaning and solid waste management workers were positive for SARS-CoV-2 during the period of community transmission of the Omicron variant. These results are alarming and suggest a high vulnerability of these workers to COVID-19. During the first weeks of 2022, a prevalence of approximately 2% of COVID-19 was estimated for the general population in the city of Aracaju [6]. It is important to highlight that workers involved in garbage collection and waste handling are historically exposed to a number of risks related to occupational health, especially in developing countries, where these professionals work outdoors and in direct contact with poorly packaged materials [7-9].

It has been shown that the risk of exposure to SARS-CoV-2 among these workers is greatest during garbage collection, mechanical handling of compactor trucks, and garbage unloading at the disposal site [10]. In addition, issues related to educational level and personal hygiene, the lack of official safety guidelines, and problems with the supply and control of the use of personal protective equipment by companies are factors that can increase the risk of contamination among these individuals. In a study carried out in the city of São Paulo between March 2020 and March 2021, a positive correlation was observed between the number of household waste collection workers with COVID-19 and the incidence of the disease on collection routes, especially in the regions

with worse socioeconomic indicators [11]. There is, therefore, a need for collective efforts involving the general population, service providers, and local government to control the spread of COVID-19 arising from the management of waste collection in cities [12].

There is evidence that education and training are key factors in preventing and reducing occupational injuries and illnesses among urban cleaning and solid waste management workers [13,14]. Furthermore, it has been observed that the perceived susceptibility to and severity of an occupational disease are positive predictors of adherence to the use of personal protective equipment [15]. However, in a context where there is a collective need for vaccination against a highly communicable disease such as COVID-19, higher levels of vaccine hesitancy have been observed among individuals with lower educational levels [16]. In our study, although 99% of workers had received the first dose of the vaccine against COVID-19, approximately 11% reported not believing in the protective effect of vaccines and fewer than 30% had completed their vaccination schedule. We found a higher prevalence of SARS-CoV-2 infection among those who lacked confidence in vaccine protection, indicating the need for an effective education program on disease prevention. Despite these findings, further studies should explore the behavioral factors that contribute to the higher prevalence of COVID-19 in this population.

In summary, this study showed a high prevalence of SARS-CoV-2 infection in urban cleaning and solid waste management workers during transmission of the Omicron variant in Northeast Brazil, with higher rates among younger individuals and among those who did not trust the protective effect of vaccines. These findings highlight the importance of COVID-19 monitoring programs among individuals at higher risk of infection, especially when social restriction measures have been relaxed in Brazil. Moreover, our results indicate the need for better guidance on preventive measures against COVID-19 in this population.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

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AUTHOR CONTRIBUTIONS

Conceptualization: Martins-Filho PR, Barboza WDS, Cavalcante TF, de Souza Araújo AA. Data curation: dos Santos JTDC, Rezende MS, de Carvalho FO, dos Reis ES, dos Santos CA, Grespan R, Corrêa CB, de Moura TR, Schimieguel DM, Quintans JDSS. Formal analysis: Martins-Filho PR, de Souza Araújo AA, Quintans-Júnior LJ. Funding acquisition: de Souza Araújo AA, Quintans-Júnior LJ. Methodology: Martins-Filho PR, Barboza WDS, Cavalcante TF, de Souza Araújo AA. Project administration: Martins-Filho PR, Barboza WDS, Cavalcante TF. Visualization: Martins-Filho PR, de Souza Araújo AA, Quintans-Júnior LJ. Writing – original draft: Martins-Filho PR, de Carvalho FO. Writing – review & editing: Martins-Filho PR, dos Santos JTDC, Rezende MS, de Carvalho FO, dos Reis ES, Barboza WDS, Cavalcante TF, dos Santos CA, Quintans-Junior LJ, Grespan R, Corrêa CB, de Moura TR, Schimieguel DM, Quintans JDSS, de Souza Araújo AA.

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BRIEF COMMUNICATION

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Dynamics of hospitalizations and in-hospital deaths from COVID-19 in northeast Brazil: a retrospective analysis based on the circulation of SARS-CoV-2 variants and vaccination coverage

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This study investigated the dynamics of hospitalizations and in-hospital deaths from coronavirus disease 2019 (COVID-19) throughout the pandemic in northeast Brazil, the Brazilian region with the worst socioeconomic indicators. In total, 141,445 cases, 8,213 hospital admissions, and 1,644 in-hospital deaths from COVID-19 were registered from March 14, 2020 to February 5, 2022. The overall rates of hospitalization and in-hospital deaths were 5.8% and 20.0%, respectively. The hospitalization and death rates significantly decreased over time, which may have been related to progress in vaccination. During the spread of the Gamma variant (January to June 2021), most hospitalized individuals were young adults, and approximately 40% of deaths occurred in this age group. During the predominance of Delta (July to December 2021), over 75% of deaths occurred among the elderly and unvaccinated or partially vaccinated individuals. This rate decreased to 42.3% during the transmission of the Omicron variant (January to February 2022), during which 34.6% of deaths were recorded among fully vaccinated individuals (2 doses) and 23.1% among those who received full vaccination and a booster. The Omicron-driven third wave was associated with a rise in the proportion of deaths among vaccinated individuals, especially among those who had not received a booster dose.

KEY WORDS: COVID-19, SARS-CoV-2, SARS-CoV-2 variants, COVID-19 vaccines

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a primarily respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with higher mortality rates in male, older people, and those with pre-existing clinical conditions, including hypertension, diabetes, and heart disease [1]. In addition, it has been shown that the COVID-19 fatality rate is higher in vulnerable populations [2,3]. In Brazil, the lack of a national policy against the disease, the increasing population mobility (including international travels and tourism), the return of face-to-face work activities, difficulties in implementing individual and community measures to mitigate COVID-19 transmission, and delays in vaccination have contributed to the emergence and spread of SARS-CoV-2 variants of concern (VOCs) across the country over time [4].

Although the clinical outcomes of patients with COVID-19 are influenced by biological, social, behavioral, and structural factors, it has also been suggested that the risks of hospitalization, inten-

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sive care unit (ICU) admission and mortality are higher among patients infected with SARS-CoV-2 VOCs than among those with the wild-type virus [5]. Moreover, there is evidence of an increased risk of hospitalization and death among unvaccinated individuals [6]. In this study, we investigated the dynamics of hospitalizations and deaths from COVID-19 throughout the pandemic in northeast Brazil, the region with the worst socioeconomic indicators in the country.

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted in the city of Aracaju, the capital of Sergipe State, northeast Brazil, from March 14, 2020 to February 5, 2022. The present study is part of the EpiSERGIPE Project, which aims (1) to monitor the epidemiological behavior of COVID-19 in Sergipe State and (2) to support evidence-informed public health decision-making.

Context

Aracaju is a coastal city located in the poorest region of the country and has a current population estimated at over 657,000 inhabitants. The first case of COVID-19 in Aracaju was identified on March 14, 2020 in a female patient with recent travel to Spain, while the first death from COVID-19 was confirmed on April 2, 2020. As of February 5, 2022, 141,445 cases (1,671 classified at hospital admission as severe or critical) and 2,461 deaths from COVID-19 were registered by the Aracaju Municipal Health Department. In Sergipe State, the COVID-19 vaccination campaign started on January 19, 2021. On June 30, 2021, the vaccination coverage of the general population was approximately 12%, while for individuals over 60 years of age it was 61.4%. At the time of writing this manuscript, the overall COVID-19 vaccination coverage was 73.1%.

Eligibility criteria and data collection

All patients residing in Aracaju with COVID-19 confirmed by polymerase chain reaction testing who were consecutively admitted to public and private hospitals in the city were included. Data on COVID-19 were extracted from the microdata catalog and official bulletins of the Aracaju Municipal Health Department. The data collected included (1) confirmed cases, (2) vaccination coverage, (3) hospitalizations (admissions, sex and age distribution, hospitalization rate, bed types [clinical beds and ICU], and length of hospital stay), and (4) in-hospital deaths. We also calculated the hospitalization rate (admissions/confirmed cases), in-hospital mortality rate (deaths/admissions), and death rate by vaccination status (fully vaccinated plus booster dose, fully vaccinated with 2 doses, and unvaccinated or partially vaccinated individuals).

Statistical analysis

The analyses were stratified into 4 periods of the pandemic according to the predominance of variants in Sergipe State: March to December 2020 (B.1, B.1.1.33, B.1.1.119, B.1.1.28), January to June 2021 (Gamma, Zeta), July to December 2021 (Delta), and January to February 2022 (Omicron). The admission date was used as a reference for the distribution of patients in each period. The hospitalization and death rates according to the periods of the pandemic were compared using the 4-sample test for equality of proportions using the Holm method for p-value adjustment. Differences in the length of hospital stay over time were analyzed using the Kruskal-Wallis test followed by the Dunn post hoc test for multiple comparisons. The p-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using the RStudio (https://www.rstudio.com/) software.

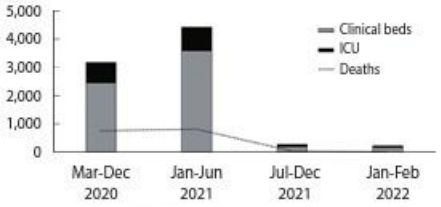
Ethics statement

The EpiSERGIPE Project was approved by the Ethics Committee of the Federal University of Sergipe (protocol No. 33095120.4.0000.5546).

RESULTS

During the study period, 141,445 cases of COVID-19 and 8,213 hospital admissions were recorded. The overall hospitalization rate was 5.8%, with significant variations across the different phases of the pandemic ($p < 0.001$). In 2020, the hospitalization rate related to COVID-19 was estimated at 5.9%. From January to June 2021, with the wide circulation of the Gamma and Zeta variants, the hospital admission rate increased to 6.9%. However, with progress in vaccination coverage from the second half of 2021, the hospitalization rates declined to 3.6% and 1.7% during the community transmission of Delta and Omicron variants, respectively. In addition, the length of stay during Omicron circulation was the shortest in the entire series (median, 4.0 days; $p < 0.001$).

Our findings showed that approximately 20% of patients hospi-



Prevalent variants	B.1, B.1.1.33, B.1.1.119, B.1.1.28	Gamma, Zeta	Delta	Omicron
Vaccination coverage (%)	0.0	11.9	71.2	73.1
In-hospital mortality rate (%)	23.2	18.4	15.5	11.6

Figure 1. Hospitalizations and in-hospital deaths from coronavirus disease 2019 at different phases of the pandemic according to the circulation of severe acute respiratory syndrome coronavirus 2. ICU, intensive care unit.

talized with COVID-19 were admitted to the ICU throughout the pandemic, with the highest ICU occupancy rate (27.1%) observed during Delta circulation ($p < 0.001$). No significant differences were observed in hospitalizations according to sex over time ($p = 0.335$). However, we found significant variations in admissions by age ($p < 0.001$). In 2020, we found a high hospitalization rate among children and adolescents (12.1%). Following a period of decline throughout 2021, the hospitalization rate in this age group increased significantly in 2022, especially for children aged 0-4 years. In relation to adults, a different epidemiological pattern was observed. Individuals aged 20-59 years had the highest hospitalization rate (58.0%) from January to June 2021, with the spread of the Gamma and Zeta variants and low vaccination coverage for the general population. Conversely, this was the period with the lowest proportion of admissions among individuals over 60 years of age (37.7%), as more than 60% of this population was already fully vaccinated. However, as of July 2021, the hospitalization rate increased among the elderly and decreased among adults aged 20-59 years as vaccination coverage expanded for this age group.

From March 14, 2020 to February 5, 2022, 1,644 in-hospital deaths from COVID-19 were recorded, and the overall mortality rate was 20%. There was a decline in the mortality rate over time, from 23.2% in the first year of the pandemic to 11.6% in February 2022 ($p < 0.001$). We observed that during Delta circulation, 88.4%

Table 1. Clinical data and distribution of hospitalizations and deaths of patients with COVID-19 throughout the pandemic

Variables	Mar to Dec 2000	Jan to Jun 2021	Jul to Dec 2021	Jan to Feb 2022
Prevalent SARS-CoV-2 variants	B.1, B.1.1.33, B.1.1.119, B.1.1.28	Gamma, Zeta	Delta	Omicron
Cases of COVID-19 (n)	55,539	64,943	7,654	13,309
Vaccination coverage at the end of the period (%)	0.0	11.9	71.2	73.1
Hospitalizations				
Admissions (n)	3,253	4,459	277	224
Sex: male	1,854 (57.0)	2,545 (57.1)	156 (56.3)	114 (50.9)
Age (yr)				
0-4	241 (7.4)	124 (2.8)	10 (3.6)	14 (6.3)
5-19	152 (4.7)	60 (1.3)	4 (1.4)	6 (2.7)
20-59	1,358 (41.8)	2,586 (58.0)	136 (49.1)	55 (24.6)
≥ 60	1,499 (46.1)	1,681 (37.7)	127 (45.9)	149 (66.4)
No information	3 (0.1)	8 (0.2)	-	-
Hospitalization rate (%)	5.9	6.9	3.6	1.7
Bed types				
Clinical beds	2,452 (75.4)	3,588 (80.5)	202 (72.9)	174 (77.7)
Intensive care unit	721 (22.2)	825 (18.5)	75 (27.1)	50 (22.3)
No information	80 (2.4)	46 (1.0)	-	-
Length of hospital stay (day)[1]	8.0 (4.0-16.0)	7.0 (4.0-12.0)	7.0 (4.0-13.3)	4.0 (2.0-7.0)[3]
In-hospital mortality data				
Deaths (n)	756	819	43	26
Sex: male	445 (58.9)	458 (55.9)	20 (46.5)	11 (42.3)
Age (yr)				
0-4	3 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
5-19	4 (0.5)	3 (0.4)	0 (0.0)	0 (0.0)
20-59	194 (25.7)	324 (39.5)	11 (25.6)	6 (23.1)
≥60	555 (73.4)	491 (60.0)	32 (74.4)	20 (76.9)
No information	-	-	-	-
Mortality rate (%)	23.2	18.4	15.5	11.6
Death rate by vaccination status (%)[2]				
Fully vaccinated plus booster dose	-	0.0	2.3	23.1
Fully vaccinated (2 doses)	-	0.0	9.3	34.6
Unvaccinated or partially vaccinated	-	100	88.4	42.3

Values are presented as number (%) or median and interquartile range (Q1–Q3).
COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[1]Patients discharged.
[2]Information retrieved from the database of the Municipal Health Department.
[3]Ninety-seven patients remained hospitalized at the time of analysis.

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of deaths occurred among unvaccinated or partially vaccinated individuals. This rate decreased to 42.3% during Omicron circulation, while 34.6% of deaths were recorded among those fully vaccinated with 2 doses and 23.1% among those fully vaccinated plus a booster dose. The mortality rates according to vaccination status were significantly different between the analyzed periods ($p < 0.001$).

Despite a reduction in the proportion of deaths among males, no significant changes were observed over time ($p = 0.130$). During the entire pandemic, at least 65% of deaths occurred among individuals over 60 years of age. The first half of 2021 was the period with the lowest in-hospital mortality rate (60.0%) for this age group ($p < 0.001$). Among adults aged 20-59 years, there was a significant increase in the proportion of deaths from 2020 (25.7%) to the first half of 2021 (39.5%) ($p < 0.001$). In February 2022, the in-hospital mortality rate for this age group was 23.1%. Eleven deaths were recorded among children and adolescents, and the majority ($n = 7$; 63.3%) were in the first year of the pandemic. The dynamics of hospitalizations and deaths from COVID-19 over time are shown in Figure 1. Table 1 presents the details of hospitalizations and deaths according to the circulation of SARS-CoV-2 variants and vaccination coverage.

DISCUSSION

The overall findings of this study showed that approximately 6% of COVID-19 patients required hospitalization, of which roughly 80% were in clinical beds and approximately 20% were in ICU beds. The in-hospital mortality rate was 20%, with a higher rate observed among males. Although the majority of hospitalized patients were adults aged 20-59 years (about 50%), more than 65% of deaths occurred in individuals over 60 years of age. The results of this study are comparable to those presented in a meta-analysis [7] involving 281,461 individuals with COVID-19 from 11 countries/regions, in which 23% of patients had severe disease, and age and male sex were associated with a higher risk of mortality. However, the ICU bed hospitalizations and mortality rates were lower than those reported in our study, which may be a result of differences in social, economic, and healthcare resources between populations.

Regarding the analyses in specific periods, we observed that during the first wave of COVID-19 in 2020, individuals over 60 years old accounted for the highest proportion of hospitalizations (approximately 46%). Moreover, this period of the pandemic was characterized by the highest in-hospital mortality rate (approximately 23%), concentrated in the oldest age group. The median length of stay was also the longest (8 days) in the entire series, with a rate of admission to ICU beds of approximately 20%. Our results highlight the critical situation of the health system in response to the demand generated by the first wave of COVID-19, especially among the individuals who were most vulnerable to the worst clinical outcomes of the disease. The lack of a national protocol for the care of patients with COVID-19, scientific denialism, overcrowding in hospitals, and the use of personnel without adequate training and experience in the first year of the pandemic may have led to increased mortality, especially in poorer regions.

The second wave of COVID-19 in Brazil, during the first half of 2021, added enormous pressure to the healthcare system with the emergence of the Gamma variant, first detected in Manaus (northern Brazil) in January 2021. A large number of hospitalizations was recorded in a short period, with a significant increase in deaths among adults aged 20-59 years and a decreased mortality rate among the elderly. Although this phase was marked by the beginning of the vaccination campaign, prioritizing health professionals and elderly people, the change in the epidemiological profile of infected patients with SARS-CoV-2 was also observed in other regions of the country [8,9] and may have been associated with the relaxation of restrictive measures and the reopening of trade and services while the country faced a SARS-CoV-2 variant that was roughly 2.5 times more transmissible than that of the first wave [10].

In Brazil, the second half of 2021 was characterized by the spread of the Delta variant, responsible for rapid growth in the number of COVID-19 cases in Europe and the United States in June 2021 [11]. Despite evidence that the Delta variant has potentially faster viral replication and higher infectiousness [12], the number of COVID-19 cases during the period of the prevalence of this variant was 88% lower than that observed during Gamma circulation, which can be explained by the progress of the vaccination campaign in Brazil. In addition, this period had a lower overall hospitalization rate and a reduction of in-hospital deaths compared to the first and second waves. However, there was a high occupancy rate of ICU beds (approximately 27%) among those who needed to be hospitalized and an increase in the in-hospital mortality rate for the elderly, especially among the unvaccinated or partially vaccinated. The Delta variant led to a higher risk of ICU admission than other variants [13], as well as increasing the risk of death in unvaccinated individuals [14].

Although the COVID-19 vaccination campaign in Brazil prevented a third wave associated with the Delta variant, the country experienced a sudden increase in COVID-19 cases in January and February 2022 due to community transmission of the Omicron variant. The Omicron variant was first detected in Brazil in late 2021 in travelers from South Africa; probably due to the relaxation of non-pharmacological containment measures and the lack of systematic surveillance among travelers throughout the country, Omicron-related cases became prevalent across the Brazilian states. In Sergipe State, the first cases were detected in January 2022, which temporally coincided with the final 3 months of our study and may explain the increase in cases in this period. Moreover, we observed a proportional increase in hospitalization rates among children, adolescents, and individuals over 60 years of age, especially in relation to clinical beds. Similar findings were found in the Unite States, where the Omicron variant was associated with less severe outcomes than Delta [15]. During this phase, the median length of stay was 4 days and the mortality rate was

approximately 12%, with most deaths occurring among the elderly and unvaccinated or partially vaccinated individuals. In addition, the spread of Omicron was accompanied by an increase in the proportion of deaths among vaccinated individuals, especially among those without a booster dose. There is emerging evidence that the Omicron variant is characterized by immune evasion and that individuals boosted with mRNA vaccines may have increased neutralizing activity against this variant [16,17].

This study showed important changes in the epidemiological profile of hospitalized patients who died from COVID-19 during the pandemic. In addition, the Omicron-driven third wave has been associated with an increase in the proportion of deaths among vaccinated individuals, especially among those who did not receive a booster dose.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

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Conceptualization: Martins-Filho PR, Barboza WDS, Cavalcante TF. Data curation: Martins-Filho PR, Barboza WDS, Cavalcante TF. Formal analysis: Martins-Filho PR, de Souza Araújo AA, Quintans-Júnior LJ. Funding acquisition: de Souza Araújo AA, Quintans-Júnior LJ. Methodology: Martins-Filho PR, Barboza WDS, Cavalcante TF. Project administration: Martins-Filho PR, Barboza WDS, Cavalcante TF. Visualization: Martins-Filho PR, de Souza Araújo AA, Quintans-Júnior LJ, Santos VS. Writing – original draft: Martins-Filho PR, Soares BDS. Writing – review & editing: Martins-Filho PR, de Souza Araújo AA, Quintans-Júnior LJ, Soares BDS, Barboza WDS, Cavalcante TF, Santos VS.

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PAN AMERICAN JOURNAL OF PUBLIC HEALTH

Brief communication

Surveillance of adverse events associated with 145 000 doses of COVID-19 vaccines in a Brazilian municipality

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ABSTRACT There is a lack of real-world surveillance studies on reports of adverse events associated with COVID-19 vaccination, as well as comparative analyses of adverse events from vaccines with different platforms. This observational, descriptive, retrospective study based on secondary data describes the adverse events following immunization (AEFIs) related to the first 145 000 doses of COVID-19 vaccines delivered in Aracaju municipality, Sergipe state, northeast Brazil. Records of AEFIs were collected using the e-SUS Notifica database for January 19 to April 30, 2021. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for AEFIs and the type of COVID-19 vaccine, either CoronaVac (Sinovac–Butantan) or Oxford–AstraZeneca (Fiocruz). A total of 474 AEFIs (32.7 events/10 000 doses) from 254 individuals were reported and analyzed, and all of them were classified as non-serious. There was an association between the use of the CoronaVac vaccine and headache (OR = 2.1; 95% CI: 1.4–3.2), pain at the injection site (OR = 9.6; 95% CI: 3.9–23.8), lethargy (OR = 5.2; 95% CI: 1.8–14.8), fatigue (OR = 10.1; 95% CI: 2.4–42.3), diarrhea (OR = 4.4; 95% CI: 1.5–12.5) and cold-like symptoms (OR = 8.0; 95% CI: 1.9–34.0). However, the proportion of individuals reporting fever was higher among those who received the Oxford–AstraZeneca vaccine (OR = 3.1; 95% CI 1.5–6.4). This population-based observational study strengthens the evidence for the safety and tolerability of the CoronaVac and Oxford–AstraZeneca vaccines used against COVID-19.

Keywords COVID-19; SARS-CoV-2; COVID-19 vaccines; drug-related side effects and adverse reactions; injection site reaction.

Mass vaccination is the most cost-effective measure to control and prevent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The available vaccines have 50–95% effectiveness in preventing severe outcomes from coronavirus disease 2019 (COVID-19) and have been shown to be safe in clinical trials (1–5). Despite adverse events following immunization (AEFIs) being well documented in vaccine trials, post-approval surveillance of these is critical to improve safety and maintain public confidence in a vaccination program (6). There is a lack of real-world surveillance studies of AEFIs associated with COVID-19 vaccination, as well as a lack of comparative analyses of adverse events from vaccines using different platforms.

This observational, descriptive, retrospective study based on secondary data describes the AEFIs related to the first 145 000

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doses of COVID-19 vaccines delivered in Aracaju municipality, Sergipe state, northeast Brazil. Aracaju is one of the poorest regions in the country, has an area of 182.2 km², and has an estimated population of 657 053 inhabitants. On March 14, 2020, the first case of COVID-19 was identified in a female patient who had traveled to Spain; on April 2, 2020, the first death from the disease was officially confirmed. At the time of writing this manuscript in 2022, SARS-CoV-2 had infected 150 303 individuals and resulted in 2558 deaths. In Brazil, CoronaVac (a Sinovac–Butantan product) was the first vaccine approved for use against COVID-19 and was delivered primarily to elderly people, health care workers and members of Indigenous communities, all of whom were considered priority groups for immunization at the beginning of the vaccination campaign. In Aracaju, the first doses of the vaccine were administered on January 19, 2021. In early February 2021, the first doses of the Oxford–AstraZeneca vaccine (produced in Brazil by Fiocruz) were administered.

Records of AEFIs were collected using the e-SUS Notifica database for January 19 to April 30, 2021. The e-SUS Notifica database was launched in Brazil on March 27, 2020, and it has been used as a passive surveillance system by public and private health professionals to notify AEFIs occurring within 30 days of vaccination. If an adverse event occurs, the patient is followed up until it resolves. For this study, information about age, sex, type of COVID-19 vaccine, and AEFIs was extracted. Adverse events were classified as serious or non-serious. Serious adverse events included death, life-threatening illness, hospitalization or prolongation of hospitalization, and permanent disability. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for associations between AEFIs and the type of COVID-19 vaccine (CoronaVac vs. Oxford–AstraZeneca). In the case of zero events, a continuity correction of 0.5 was used. Analyses were performed using JASP software version 0.13 (JASP, Amsterdam, the Netherlands).

Between January 19 and April 30, 2021, 145 133 doses of COVID-19 vaccine were administered: 85 587 were CoronaVac and 59 546 were Oxford–AstraZeneca. A total of 474 AEFIs were reported (32.7 events/10 000 doses) from 254 individuals (mean age: 41 years; standard deviation: 9.8; 208/254 [81.9%] female) and analyzed, and all of them were classified as non-serious events. Of the 254 individuals with AEFIs, 221 (87%) received CoronaVac and 33 (13%) received Oxford–AstraZeneca. The most common AEFIs were headache (7.7 events/10 000 doses), pain at the injection site (5.1/10 000 doses), myalgia or arthralgia (3.3/10 000 doses), nausea or vomiting (2.6/10 000 doses), and fever (2.4/10 000 doses). We found an association between the use of CoronaVac and headache (OR = 2.1; 95% CI: 1.4–3.2; $P < 0.001$), pain at the injection site (OR = 9.6; 95% CI: 3.9–23.8; $P < 0.001$), lethargy (OR = 5.2; 95% CI: 1.8–14.8; $P = 0.002$), fatigue (OR = 10.1; 95% CI: 2.4–42.3; $P = 0.002$), diarrhea (OR = 4.4; 95% CI: 1.5–12.5; $P = 0.006$) and cold-like symptoms (OR = 8.0; 95% CI: 1.9–34.0; $P = 0.005$). However, the proportion of individuals reporting fever was higher among those who received the Oxford–AstraZeneca vaccine (OR = 3.1; 95% CI: 1.5–6.4; $P = 0.002$) (Table 1).

In this real-world surveillance study, we observed a rate of approximately 33 adverse events per 10 000 doses of COVID-19 vaccine during the first 3 months of the vaccination campaign in a Brazilian municipality. Despite the rate of AEFIs being lower than that shown in previous Phase 1 and 2, randomized controlled trials (7, 8), our findings also demonstrated that adverse events were mild and self-limited and included primarily headache and local pain at the injection site. Moreover, no life-threatening complications were reported, which indicates that these vaccines are well tolerated and have minor safety issues.

TABLE 1. Association between adverse events following immunization and type of COVID-19 vaccine, Brazil, 2021

Type of adverse event following immunization	Type of COVID-19 vaccine						OR (95% CI)	*P* value
	Both types (*N* = 145 133 doses)		CoronaVac (Sinovac–Butantan) (*n* = 85 587 doses)		Oxford–AstraZeneca (Fiocruz) (*n* = 59 546 doses)			
	n	No. of events/ 10 000 doses	*n*	No. of events/ 10 000 doses	*n*	No. of events/ 10 000 doses		
Headache	112	7.7	84	9.8	28	4.7	2.1 (1.4–3.2)	< 0.001
Pain at injection site	74	5.1	69	8.1	5	0.8	9.6 (3.9–23.8)	< 0.001
Myalgia or arthralgia	48	3.3	27	3.2	21	3.5	1.1 (0.6–2.0)	0.702
Nausea or vomiting	38	2.6	26	3.0	12	2.0	1.5 (0.8–3.0)	0.240
Fever	35	2.4	11	1.3	24	4.0	3.1 (1.5–6.4)	0.002
Drowsiness or lethargy	34	2.3	30	3.5	4	0.7	5.2 (1.8–14.8)	0.002
Fatigue	31	2.1	29	3.4	2	0.3	10.1 (2.4–42.3)	0.002
Diarrhea	29	2.0	25	2.9	4	0.7	4.4 (1.5–12.5)	0.006
Cold-like symptoms	25	1.7	23	2.7	2	0.3	8.0 (1.9–34.0)	0.005
Abdominal pain	20	1.4	16	1.9	4	0.7	2.8 (0.9–8.3)	0.067
Local reaction (erythema, induration, swelling)	16	1.1	10	1.2	6	1.0	1.2 (0.4–3.2)	0.774
Dizziness	9	0.6	8	0.9	1	0.2	5.6 (0.7–44.5)	0.106
Shortness of breath	2	0.1	2	0.2	0	0.0	3.5 (0.2–72.5)	0.421
Lymphadenopathy	1	0.1	1	0.1	0	0.0	2.1 (0.1–51.2)	0.652

CI: confidence interval; OR: odds ratio.

Although associations between specific vaccine platforms and adverse events are poorly understood, viral vector vaccines carry information that might be critical for the enhancement of proinflammatory cytokines, leading to an intense systemic response (9). In this study, immunization with Oxford–AstraZeneca – a replication-deficient chimpanzee adenovirus–vector vaccine encoding the SARS-CoV-2 Spike glycoprotein – was strongly associated with the occurrence of fever. This finding is in agreement with a previous study from Thailand that found a higher frequency of individuals reporting fever after vaccination with the chimpanzee adenovirus–vector vaccine compared with those receiving a whole-cell inactivated vaccine (10). However, in our study, individuals receiving the inactivated SARS-CoV-2 vaccine were more likely to experience headache, local pain, lethargy, fatigue, diarrhea and cold-like symptoms.

Our results should be interpreted with caution due to the inherent limitations of spontaneous (passive) surveillance and the lack of analysis of sex- and age-based differences regarding the adverse events. However, this population-based observational study reinforces the safety and tolerability of the CoronaVac and Oxford–AstraZeneca vaccines used against COVID-19.

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Factors Associated with Mortality among Hospitalized Patients with COVID-19: A Retrospective Cohort Study

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Abstract. Information on the risk factors for COVID-19 mortality in low- and middle-income countries is still scarce. In this retrospective cohort study, we analyzed the factors associated with COVID-19 mortality in hospitalized patients in a poor area of Brazil. Logistic regression was used to identify factors independently associated with mortality, including gender, age, and the presence of underlying medical conditions. A total of 1,207 patients were included in the analysis, and a 1.5-fold increase in COVID-19 mortality was found among patients aged > 65 years with hypertension and diabetes (odds ratio [OR]: 1.50, 95% CI: 1.02–2.19). Moreover, infectious disease (OR: 4.31, 95% CI: 1.39–13.39), kidney disease (OR: 2.59, 95% CI: 1.27–5.27), and heart disease (OR: 2.00, 95% CI: 1.31–3.04) were also predictive for COVID-19 in-hospital death. This large cohort provides important data on potential factors associated with COVID-19 mortality in Brazil.

INTRODUCTION

SARS-CoV-2 is an emerging RNA virus associated with a severe acute respiratory disease known as COVID-19. Globally, SARS-CoV-2 infected more than 50 million people and caused more than 1.2 million deaths until November 9, 2020. In high-income countries, COVID-19 mortality has been higher in men, older people, and those with some comorbidity, including hypertension, diabetes, and cardiovascular disease.[1] However, information on the risk factors in low- and middle-income countries is still scarce. Herein, we report the factors associated with COVID-19 mortality in hospitalized patients in a poor area of Brazil.

METHOD

This retrospective cohort study enrolled all adults with PCR-confirmed COVID-19 who were consecutively admitted to public and private hospitals in Aracaju, Sergipe state, Northeast Brazil, from March 17 to July 14, 2020. Aracaju is a coastal city located in the poorest region in a country marked by large regional disparities. This city has an estimated population of 657,053 inhabitants and a high proportion of low-income households (42.9%). Recently, it was found that neighborhoods with poor living conditions in Aracaju are more likely to have higher COVID-19 fatality rates.[2]

Data on COVID-19 cases and deaths were extracted from the microdata catalog and official bulletin of the Municipal Secretariat of Health. We excluded patients with incomplete information, pregnant women, patients aged 18 years and younger, and those treated in hospital outside of Aracaju. Data collected included the outcome of interest (death) and potential factors associated with COVID-19 mortality: gender, age, and the presence of underlying medical conditions (gastrointestinal disease, chronic pulmonary disease, asthma, neurodegenerative disease, stroke, hypothyroidism, cancer, non-HIV immunosuppressive disease, obesity, infectious disease, kidney disease, heart disease, hypertension, and diabetes).

Data were presented as absolute and relative frequencies, and comparisons between survivors and non-survivors were expressed as odds ratio (OR) with 95% CIs. Logistic regression was used to identify factors independently associated with mortality. First, a univariate model was performed. Afterward, interaction was checked to control the relationship between covariates and their effect on the outcome. Finally, we included in multivariate analyses with backward selection all factors that have shown a relaxed P-value ≤ 0.30. Two multivariate models were developed. Model 1 included a standard logistic regression, and model 2 incorporated interaction for age, hypertension, and diabetes. P-values < 0.05 were considered statistically significant. All data were de-identified, and analyzes were performed using JASP software version 0.13 (JASP Team, Amsterdam, Netherlands).

RESULTS

A total of 1,207 of 1,632 patients initially considered met the eligibility criteria and were included in the analysis. The median (IIQ) age was 60 (46–73) years. Seven hundred twenty-four (60.0%) were men, and 708 (58.7%) patients had at least one coexisting condition (Table 1).

Overall, 353 patients (29.2%) died. The median age of survivors was lower than that of non-survivors (median [IIQ]: 57 [43–70] versus 68 [55–79]; $P < 0.001$). The univariate analysis identified eight covariates as candidates for the multivariate model, including age > 65 years, non-HIV immunosuppressive disease, obesity, infectious disease, kidney disease, heart disease, hypertension, and diabetes (Table 1).

The standard multivariate regression analysis showed that COVID-19 mortality was significantly associated with age > 65 years (OR: 2.76, 95% CI: 2.12–3.60), following underlying medical conditions: infectious disease (OR: 5.26, 95% CI: 1.66–16.71), kidney disease (OR: 2.60, 95% CI: 1.24–5.42), and heart disease (OR: 1.67, 95% CI: 1.08–2.57). By adding interactions, we found that mortality was increased 1.5-fold among patients aged > 65 years with hypertension and

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TABLE 1
Results of univariate logistic regression analysis of association between clinical factors and death in patients with COVID-19

Covariates	Survivors (n = 854), n (%)	Non-survivors (n = 353), n (%)	Odds ratio	95% CI	P-value*
Gender (male)	513 (60.1)	211 (59.8)	0.99	0.77–1.27	0.924
Age > 65 years	283 (33.1)	203 (57.5)	2.73	2.12–3.52	< 0.001
Gastrointestinal disease	11 (1.3)	3 (0.8)	0.66	0.18–2.37	0.521
Chronic pulmonary disease	28 (3.3)	12 (3.4)	1.04	0.52–2.07	0.915
Asthma	11 (1.3)	3 (0.8)	0.66	0.18–2.37	0.521
Neurodegenerative disease	17 (2.0)	9 (2.5)	1.29	0.57–2.92	0.544
Stroke	28 (3.3)	14 (4.0)	1.22	0.63–2.34	0.554
Hypothyroidism	14 (1.6)	6 (1.7)	1.04	0.40–2.72	0.940
Cancer	28 (3.3)	14 (4.0)	1.22	0.63–2.34	0.554
Non-HIV immunosuppressive disease	10 (1.2)	7 (2.0)	1.71	0.65–4.52	0.282
Obesity	77 (9.0)	23 (6.5)	0.70	0.43–1.14	0.153
Infectious disease	5 (0.6)†	8 (2.3)‡	3.94	1.28–12.12	0.017
Kidney disease	15 (1.8)	18 (5.1)	3.00	1.50–6.03	0.002
Heart disease	56 (6.6)	46 (13.0)	2.14	1.42–3.22	< 0.001
Hypertension	308 (36.1)	143 (40.5)	1.21	0.94–1.56	0.137
Diabetes	209 (24.5)	102 (28.9)	1.25	0.95–1.66	0.110

* Variables with relaxed P-value ≤ 0.30 were included in the multivariate analysis with backward selection.
† Survivors with infectious disease (HIV: 1, visceral leishmaniasis: 1, tuberculosis: 1, bacterial infection: 2).
‡ Non-survivors with infectious disease (HIV: 3, lepromatous leprosy: 4, tuberculosis: 1).

diabetes (OR: 1.50, 95% CI: 1.02–2.19). In this model, infectious disease (OR: 4.31, 95% CI: 1.39–13.39), kidney disease (OR: 2.59, 95% CI: 1.27–5.27), and heart disease (OR: 2.00, 95% CI: 1.31–3.04) remained predictive for COVID-19 in-hospital death (Table 2).

DISCUSSION

COVID-19 mortality has been high among critically ill patients and varies widely according to country; population characteristics including biological, environmental, and socioeconomic factors; social isolation policies; and health-system capacity. As other reports, older age and people with kidney and heart diseases were at a higher risk of death.[1,3,4] In addition, this cohort identified some novel patient-level factors associated with COVID-19 mortality, including infectious diseases coinfection and the interaction between older age and combined hypertension and diabetes.

In Brazil, one in five Brazilian adults has two or more comorbidities[5] which may increase the susceptibility to COVID-19 mortality. The pivotal link between SARS-CoV-2 and downregulation of angiotensin-converting enzyme-2 in people with multiple comorbidities especially diabetes and hypertension may be a critical role in the overproduction of pro-inflammatory cytokines and COVID-19 severity.[6] In addition to the relationship between older age and comorbidities, people in poor communities are less likely to have access to health care and social protection, and live in crowded homes with inadequate sanitation and hygiene, which increase the risk for COVID-19 transmission and death.[2]

Although only 1.0% of patients were coinfected with some infectious disease and COVID-19, there was an increased risk of death. Some infectious diseases can cause increased levels of inflammatory cytokines.[7] The dysregulated immune response in individuals with severe COVID-19 seems to be associated with a cytokine storm. However, the interaction between COVID-19 and other infectious diseases is highly complex, and further epidemiological and immunological studies should be performed.

Although we could not assess effects of other important variables, such as laboratory findings, respiratory support, chronic medications, and acute organ injuries during hospitalization,

TABLE 2
Results of the multivariate logistic regression analyses

	Standard analysis		Interaction analysis	
Covariates	OR (95% CI)	P-value	OR (95% CI)	P-value
Age > 65 years	2.76 (2.12–3.60)	< 0.001	–	*
Non-HIV immunosuppressive disease	–	NS	–	NS
Obesity	–	NS	–	NS
Infectious disease	5.26 (1.66–16.71)	0.005	4.31 (1.39–13.39)	0.012
Kidney disease	2.60 (1.24–5.42)	0.011	2.59 (1.27–5.27)	0.009
Heart disease	1.67 (1.08–2.57)	0.021	2.00 (1.31–3.04)	0.001
Hypertension	–	NS	–	*
Diabetes	–	NS	–	*
Age > 65 years × hypertension × diabetes	–	*	1.50 (1.02–2.19)	0.039
Model summary				
BIC	1,417.28	–	1,467.84	–
BS	0.191	–	0.201	–
AUC	0.654	–	0.588	–

AUC = area under the curve: measure of discriminatory performance where higher values indicate better performance; BIC = Bayesian information criterion: metric used for the comparison of regression models; BS = Brier score: metric used for overall model performance in which scores range from 0 for a perfect model to 0.25 for a non-informative model; NS = nonsignificant; OR = odds ratio. Data are given as OR and 95% CI.
* Not included in the model.

this large cohort provides data on potential factors associated with COVID-19 mortality from a poor area in Brazil. As risk factors may vary across populational groups, further studies in low- and middle-income cities should be performed to better understand what factors are associated with COVID-19 mortality.

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Clinical and epidemiological aspects of patients infected with SARS-CoV-2 variants: a case-control study

Aspectos clínicos e epidemiológicos de pacientes infectados com variantes do SARS-CoV-2: um estudo caso controle

Aspectos clínicos y epidemiológicos de pacientes infectados con variantes del SARS-CoV-2: un estudio de casos y controles

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Abstract
Objective: To compare the clinical outcomes of patients infected with SARS-CoV-2 variants with patients infected with the original strain. Methods: This is a case control study comparing cases of COVID-19 patients infected with SARS-CoV-2 variants of concern identified by genomic sequencing, with a control group of 62 patients randomly selected from a COVID-19 database of patients diagnosed prior to the emergence of these variants. Findings: In the 40 patients infected with variants, the predominant (52.5%) was P.1 variant. The variant group presented more arthralgia (p=0.015), hyporexia (p=0.006), nausea/vomiting (p=0.048), and mental confusion (p=0.029), the last not identified in the control group. There were no significant differences in comorbidities or demographic data between the groups. Severe disease, according to the WHO Clinical Progression Scale, was identified only in those infected with the variants, as well as high-flow oxygen therapy and ICU admission (p=0.05). The two deaths reported in the study were in patients infected with the variants. Conclusions: The worst outcomes were observed in the group infected with SARS-CoV-2 variants, although no significant differences in comorbidities or demographics date were observed between the groups.
Keywords: Case-control studies; Signs and symptoms; Virus infection, COVID-19.

Resumo
Objetivo: Comparar os desfechos clínicos de pacientes infectados com variantes dos SARS-CoV-2 com pacientes infectados com a cepa original. Métodos: Este é um estudo caso controle que compara casos de pacientes com COVID-19 infectados com variantes de preocupação do SARS-CoV-2, identificadas por sequenciamento genômico, com um grupo controle de 62 pacientes selecionados aleatoriamente de um banco de dados de pacientes com COVID-19 diagnosticados previamente ao surgimento dessas variantes de preocupação. Resultados: Nos 40 pacientes infectados com as variantes, a forma predominante foi a variante P.1 (52,5%). O grupo infectado por variantes apresentou mais artralgia (p=0,015), hiporexia (p=0,006), náusea/vômito (p=0,048) e confusão mental (p=0,029), sendo esta última não identificada no grupo controle. Não houve diferenças significativas entre os grupos quando comparados comorbidades ou dados geográficos. Forma grave da doença, de acordo com a Escala de Progressão da OMS, foi identificada somente naqueles infectados com as formas variantes, assim como o uso de oxigenoterapia de alto fluxo e admissão na UTI (p=0,05). As duas mortes reportadas no estudo foram em pacientes infectados com formas variantes do vírus. Conclusões: Os piores desfechos foram observados no grupo infectado com variantes do SARS-CoV-2, apesar de não haver diferenças significativas nas comorbidades ou dados demográficos entre os grupos.
Palavras-chave: Estudos de casos e controles; Sinais e sintomas; Infecção viral COVID-19.

Resumen
Objetivo: Comparar los resultados clínicos de los pacientes infectados con variantes del SARS-CoV-2 con los pacientes infectados con la cepa original. Métodos: Se trata de un estudio de casos y controles que comprende casos de pacientes con COVID-19 infectados con variantes de la preocupación por SARS-CoV-2, identificados por secuenciación genómica, con un grupo control de 62 pacientes seleccionados aleatoriamente de una base de datos de pacientes con COVID-19 diagnosticados antes de la aparición de estas variantes de preocupación. Resultados: En los 40 pacientes infectados con las variantes, la forma predominante fue la variante P.1 (52,5%). El grupo infectado con variantes presentó más artralgia (p=0,015), hiporexia (p=0,006), náuseas/vómitos (p=0,048) y confusión mental (p=0,029), no identificándose esta última en el grupo control. No hubo diferencias significativas entre los grupos cuando se compararon las comorbilidades o los datos geográficos. La forma grave de la enfermedad, según la Escala de Progresión de la OMS, se identificó solo en aquellos infectados con formas variantes, así como el uso de oxigenoterapia de alto flujo y el ingreso en la UCI (p = 0,05). Las dos muertes reportadas en el estudio fueron en pacientes infectados con formas variantes del virus. Conclusiones: Los peores resultados se observaron en el grupo infectado con variantes del SARS-CoV-2, aunque no hubo diferencias significativas en las comorbilidades ni en los datos demográficos entre los grupos.
Palabras clave: Estudios de casos y controles; Signos y síntomas; Infección por el virus de la COVID-19.

1. Introduction

The SARS-CoV-2 virus was identified in December 2019 in Wuhan province, China, being responsible for cases of mild disease to atypical and potentially fatal pneumonia, especially in the elderly (Leung, 2020). The unrestrained worldwide spread of SARS-CoV-2 has allowed the emergence of several mutations and new dominant variants, some of them have been designated as Variants of Concern (VOC) (Guo et al., 2021). The first VOC identified was B.1.1.7 in United Kingdom, with the rapid spread of this variant around the world being remarkable (Tang et al., 2021). The second one, B.1.351, emerged in South Africa and bring concern about increased infectivity (Tegally et al., 2021). In Brazil, the uncontrolled spread of SARS-

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CoV-2 led to emergence of two VOC, VOC P.1 and the VOC P.2 (Castro et al., 2021). Both variants were associated with cases of reinfection, decrease of efficiency of some vaccines and severe cases, contributing with the devasting second wave in Brazil (Faria et al., 2021; Zeiser et al., 2022). Due to the ongoing pandemic situation, other SARS-CoV-2 variants continues to be identified and related to increase of infectivity and disease severity (Aleem et al., 2021).

COVID-19 continues to be a challenge worldwide. Analysis of clinical presentation, especially in cases of infection with the virus variants, provides subsidies for greater knowledge of the disease, both by raising data for clinical suspicion, as well as to guide possible treatments and control measures to be adopted by the administrators (Ong et al., 2021).

The present study reports the clinical-epidemiological profile of 40 COVID-19 patients infected by variants, comparing the clinical course and outcomes of these cases with a control group of 62 patients randomly selected from a COVID-19 database of patients diagnosed prior to the emergence of these variants.

2. Methodology

Ethical aspects

This study was approved by the research ethical board of the Federal University of Sergipe (CAAE 31079720.5.0000.5546) and followed the recommendations of Resolution 466/2012 from the National Health Council, Ministry of Health, Brazil.

Study design and clinical sampling

This is a case-control, clinical-epidemiological study, including patients who were RT-qPCR positive for SARS-CoV-2. The paper organization was based in guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Due to social distancing and the difficulties to face-to-face care during the critical period of the pandemic, the 'Monitora Corona' project was created to follow-up patients by daily telephone calls. In this study, the control group was composed of individuals who were infected by the original strain of SARS-CoV-2, during April to July 2020, before the emergence of variants, randomly extracted from Monitora Corona project. Meanwhile, the case group was selected from patients with RT-qPCR positive to SARS-CoV-2, during September to October 2021, and diagnosed by the Central Public Health Laboratory of Sergipe (LACEN-SE), reference and certified for diagnosis of COVID-19 in the State. The identification of virus variants was made by viral genome sequencing by the Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, the National laboratory of reference and certified for diagnosis of COVID-19. The methods and techniques for laboratorial diagnostic and sequencing are from national network of surveillance of COVID-19 and were previously published (Faria et al., 2021; Lamarca et al., 2021; Naveca et al., 2021).

To minimizing possible discrepancies in clinical manifestations, all patients are from same state, Sergipe, Brazil, aiming a more homogeneous genetic population. Demographical, epidemiological, and clinical data were collected from these patients by a semi-structured interview, using the same questionnaire for both case and control groups. Both groups were also submitted to the same classification during the interviews, according to the WHO Clinical Progression Scale, registered on the WHO International Platform (Marshall et al., 2020).

Statistical analysis

Statistical analysis was performed using the SPSS statistical program (version 26.0 for Windows). Different tests were used, according to the obtained data, including Bootstrap. For continuous variables: Gaussian distribution was evaluated by Pearson's and Shapiro-Wilk normality tests and groups were compared by Student T test or Mann-Whitman U test. For

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categorical data: the association was tested using a 95% confidence interval (CI) using Fisher's Exact Test with data considered statistically significant with values of $p \leq 0.05$.

3. Results

The present study recruited a total of 102 patients with positive RT-qPCR for SARS-CoV-2 from April 2020 to June 2021. The CT values found in the RT-qPCR analyzed in the study, range from 11 to 29, confirming the positivity for the coronavirus with a high viral load. Most samples (80.0%) were collected between days 1 and 5 of the disease, the most suitable period for estimating the viral load.

Most patients were female (N=63, F=61.8%), 14 to 73 years old (average of 41.8 years, ± 12.3 DP), and work in industry and commerce sector (N=47, F=46.0%). The most common comorbidities found were Systemic Arterial Hypertension (N=23, F=22.5%) and Obesity (N=21, F=20.6%). The most prevalent blood type was O+ (N=37, F=36.2%) followed by A+ (N=16, F=16.7%). Azithromycin and systemic corticotherapy were used in more than half of the patients (N=54, F=52.9% for Azithromycin and N=53, F=51.9% for systemic corticoids). The epidemiological and clinical characteristics found in patients infected with variants of SARS-CoV-2 are like the total group described.

Table 1 shows differences in epidemiological and clinical aspects on admission and clinical outcome according to the WHO progression scale between case group, patients with SARS-CoV-2 variants, and control group, patients infected with the original strain. There is a statistical relevant higher frequency of healthcare professionals in the control group. As for associated diseases, dyslipidemia was more frequent in the case group, from the variants (p=0.011). No statistical significance was identified between the groups in respect to the treatments used.

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Table 1. Comparison of demographic, clinical data on admission and clinical outcome according to the WHO progression scale between COVID-19 patients infected by SARS-CoV-2 variants and a control group infected with the original variant from a state of Northeast, Brazil.

Variables	Variant Group (n=40) % (n)	Control Group (n=62) % (n)	*p* value*
Age (Mean ± SD)	42.8 ± 11.9	41.1 ± 12.5	0.922
Females	60.0 (24)	62.9 (39)	0.836
Healthcare workers	15.0 (6)	40.3 (25)	0.001
Blood type A	21.6 (8)	19.4 (12)	0.873
Blood type O	47.5 (19)	43.6 (27)	0.873
Associated diseases (Systemic Arterial Hypertension, Diabetes, Obesity and Asthma)	32.5 (13)	21.0 (13)	0.206
Dyslipidemia	35.0 (14)	14.5 (9)	0.011
Azytromycin treatment	65.0 (26)	45.2 (28)	0.050
Corticoid treatment	45.0 (18)	56.5 (35)	0.258
Clinical Manifestations			
Musculoskeletal system			
Asthenia	57.5 (23)	58.1 (36)	0.955
Myalgia	67.5 (27)	59.7 (37)	0.425
Arthralgia	**47.5 (19)**	**24.2 (15)**	**0.015**
Digestive system			
Odynophagia	50.0 (20)	37.1 (23)	0.198
Dysgeusia	65.0 (26)	64.5 (40)	0.960
Anosmia	65.0 (26)	59.7 (37)	0.589
Hyporexia	**60.0 (24)**	**32.3 (20)**	**0.006**
Diarrhea	35.0 (14)	30.6 (19)	0.646
Abdominal pain	35.0 (14)	19.4 (12)	0.077
Nausea/vomiting	**35.0 (14)**	**17.7 (11)**	**0.048**
Respiratory system			
Dry cough	75.0 (30)	74.2 (46)	0.927
Productive cough	27.5 (11)	12.9 (8)	0.065
Dyspnea	40.0 (16)	29.0 (18)	0.251
Sneeze/runny nose	57.5 (23)	46.8 (29)	0.290
Nervous system			
Headache	72.5 (29)	87.1 (54)	0.065
Dizziness	37.8 (14)	19.4 (12)	0.077
Mental confusion	**7.5 (3)**	**0 (0)**	**0.029**
Others			
Fever	65.0 (26)	50.0 (31)	0.136
Skin lesions	7.5 (3)	11.4 (7)	0.530
WHO Clinical Progression Scale			
Ambulatory mild disease	91.9 (37)	100 (62)	0.050
Moderate disease	2.7 (1)	0 (0)	0.374
Severe disease	5.4 (2)	0 (0)	0.050
Clinical evolution and outcome			
Hospitalization	10.0 (4)	4.8 (3)	0.271
Oxygen therapy high flow	7.5 (3)	0 (0)	0.050
Intensive care unit admission	7.5 (3)	0 (0)	0.050
Mechanical ventilation	5.0 (2)	0 (0)	0.146
Death	5.0 (2)	0 (0)	0.137

* Fisher's Exact Test. Source: Authors.

Patients infected with the new variants presented a higher frequency of symptoms associated with the central nervous system. The symptom of dizziness was observed in 37.8% of patients infected with variants versus 19.4% in the control group, although not statistically significant (p = 0.077). However, mental confusion was only identified in patients infected with variants, as compared to the control group (7.5 vs 0, p = 0.029). The variant group had also higher frequency of arthralgia (47.5

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vs 24.2%, p = 0.015), hyporexia (60 vs 32.3%, p = 0.006), Nausea/vomiting (35 vs 17.7%, p = 0.048). Although not statistically significant, the variant group also presented higher frequency of important respiratory symptoms, such as productive cough (27.5 vs 12.9%, p = 0.065). There were no asymptomatic cases in this study.

Clinical outcomes, according to the WHO Clinical Progression Scale criteria, it was observed moderate to severe cases only in the group of patients infected with the variants, including the two deaths identified in the study. Seven cases of hospitalization were identified in the studied patients, four (10%) in the variant group and three (4.8%) in the control group. However, these 3 patients from the control group that were hospitalized were classified as mild disease but were hospitalized to perform exams due to comorbidities. From these, only three of the case group (7.5%) evolved to high-flow oxygen therapy and admission to the Intensive Care Unit, and 2 (5.0%) evolved to mechanical ventilation and death. These 2 deceased patients had obesity and dyslipidemia in common.

The frequency of the SARS-CoV-2 variants found by the viral genome sequencing was analyzed and some of the major symptoms presented by the patients, according to the virus variant is shown in Table 2. Higher frequency of the P.1 variant was observed, representing more than half of the virus samples analyzed (52.5%). When the main clinical manifestations were analyzed, according to the type of variant, the patients infected with the P.1 variant presented a higher frequency of hyporexia, nausea/vomiting and arthralgia. The symptom of mental confusion was not present in patients infected by the P.1 variant, but it was more frequent in variant P.2.

Table 2. Frequency of clinical manifestations, evolution and outcome observed in the group infected with variants

Clinical manifestations, evolution, and outcome	P.1 (Gamma) N=21 (52.5%)	P.2 (Zeta) N = 7 (17.5%)	B.1.617.2 (Delta) N = 3 (7.5%)	Other variants N = 9 (22.5%)	*p value*[a]
Arthralgia, **% (n)**	27.5 (11)	5.0 (2)	0 (0)	15.0 (6)	0.015
Hyporexia, **% (n)**	30.0 (12)	12.5 (5)	5.0 (2)	12.5 (5)	0.006
Nausea/vomiting, **% (n)**	15.0 (6)	7.5 (3)	5.0 (2)	7.5 (3)	0.048
Mental confusion, **% (n)**	0 (0)	5.0 (2)	0 (0)	2.5 (1)	0.029
Oxygen therapy high flow	5.0 (2)	0 (0)	0 (0)	2.5 (1)	0.795
Intensive care unit admission	5.0 (2)	0 (0)	0 (0)	2.5 (1)	0.795
Mechanical ventilation	5.0 (2)	0 (0)	0 (0)	0 (0)	0.928
Death	5.0 (2)	0 (0)	0 (0)	0 (0)	0.928

[a] Fisher's Exact Test. Source: Authors.

4. Discussion

The present study reports the clinical-epidemiological profile of 40 patients infected with SARS-CoV-2 variants, comparing the clinical course and outcome of these cases with a control group of 62 patients infected previously to the variants emerged. Our analyzes found similar epidemiological profiles in the control and in the case group. Both groups have a higher frequency of women, and a similar average of age. The prevalence of health professionals in the control group may be related to the fact that they were more exposed at the beginning of the pandemic. The frequency of comorbidities is like what it is expected in the general population, portraying no selection bias, and no differences were observed in respect to comorbidities between the groups. It was found a lower frequency of obesity than in the last census, when an average of 40% of obese adults was detected (Ministério da Saúde, 2020). This factor can have an impact on the analysis of outcomes, since it is known to be a group with greater aggravation and higher mortality, that may overcome the virus variant aspect itself (Graham et al., 2021).

The greater infectivity of one variant in relation to another may be connected to the ability of the virus to escape from the immune system, which can also cause a change in clinical presentation. But it is still unclear how is the impact of such

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differences in the viral behavior, pathophysiology, and the mortality, in relation to the original genome (Tao et al., 2021). The study of clinical presentation and outcome is essential as a strategy to investigate the capacity of variants to escape acquired immunity and the possible response of discovered vaccines (Hemmer et al., 2021).

No evidence of an association between variant infection and the total number of symptoms reported by patients was found, as well as no relationship between differences in disease duration. This pattern was also evidenced in other studies in the literature (Graham et al., 2021; Tao et al., 2021). In the case group, it was observed more atypical manifestations compared to those reported in the first cases of Wuhan, such as abdominal pain, arthralgia, hyporexia and mental confusion, which may suggest virus adaptations to human being and infect of new cell groups, causing new clinical manifestations (Hemmer et al., 2021). A meta-analysis study with reports from different countries found neurological manifestations of COVID in 73% of hospitalized patients (Correia et al., 2020). Dizziness and mental confusion were symptoms reported in all of them (Espíndola et al., 2020). In our study, mental confusion was a symptom reported only in the variant group, even with a lower number of patients.

Regarding to clinical evolution and outcome, it is noteworthy that in both groups we found a hospitalization rate, although the hospitalization of the control group was not related to COVID-19 severity, since they were all classified as mild disease, and moderate to severe cases were present only in the case group. The need of oxygen and a lethality rate were observed only in the patients infected by the variants. However, these numbers were below the national (Lamarca et al., 2021) and international average for COVID-19 (Graham et al., 2021), which may be connected to the access and quality of the healthcare provided to the patients from this study, who were monitored daily by phone.

Studies in other countries have shown the association of infection by variants with an increased risk of mortality (Aleem et al., 2021). However, in Brazil, this association was not evidenced (Naveca et al., 2021). Although there were no significant differences in comorbidities or demographic data between the groups in the present study, maybe because of the low number of patients included, it is not possible to define the role of the variants itself in the induction of the most severe cases, including in the deaths. Both deaths reported in this study, occurred in patients with severe obesity and dyslipidemia.

The study of the genetics of SARS-CoV-2 brings a look at the capacity of each variant to become dominant through adaptations (Maury et al., 2021). The number of analyzed cases are still limited due to the few virus samples isolated that are submitted to genomic analysis. However, efforts to make correlation of genomics with the analysis of clinical data can provide subsidies for the study of the behavior of new viruses and guide treatments and vaccine efficacy (Chakraborty et al., 2021). Moreover, genomic data available are necessary to better comprehension of pandemic, but data accuracy is also important (Abbud & Castilho, 2022).

5. Conclusion

Therefore, this study reports differences between the clinical course and outcome of patients infected with SARS-CoV-2 variants compared to patients infected with the original strain. Some symptoms were predominant in patients infected by variants, as arthralgia, hyperoxia, nausea/vomiting and mental confusion. There was no significant difference in comorbidities or demographic data between the groups. These results, besides their limitation, contributes to better comprehension of viral behavior and disease management.

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