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Pandemic Preparedness: COVID-19, Mpox, Nipah Virus and Smallpox, A Study of Transmission, Mortality, and Vaccination Strategies

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Article

Pandemic Preparedness: COVID-19, Mpox, Nipah Virus and Smallpox, a Study of Transmission, Mortality, and Vaccination Strategies

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Summary box

- What is already known on this topic

  Pandemics caused by emerging infectious diseases like COVID-19, Mpox, Nipah, and Smallpox challenge global health systems due to varied transmission dynamics, mortality rates, and vaccine access.

- What this study adds

  This comparative analysis of COVID-19, Mpox, Nipah virus, and Smallpox identifies key differences in transmissibility, fatality, and vaccine strategy, with an emphasis on implications for LMICs and global preparedness.

- How this study might affect research, practice or policy

  The findings support global health policy efforts toward equitable vaccine distribution, enhanced surveillance for zoonotic spillovers, and development of scalable preparedness frameworks for emerging pathogens.

Abstract

Objective: To compare the transmission dynamics, mortality rates, and vaccination strategies of COVID-19, Mpox, Nipah virus, and Smallpox, and assess their implications for pandemic preparedness, particularly in low- and middle-income countries (LMICs). Methods: Structured review using WHO, CDC, and PubMed sources to analyze transmission (R0), mortality, and vaccine efficacy. Special attention was given to smallpox vaccine complications in vulnerable populations. Results: COVID-19 exhibited the highest transmissibility, while Nipah showed the highest mortality. ACAM2000 had more complications than JYNNEOS in pediatric and immunocompromised populations. Equity and safety varied significantly. Interpretation: Preparedness demands scalable vaccination, global coordination, and surveillance, particularly in LMICs. Tailored vaccine strategies for vulnerable groups are vital to pandemic resilience.

Abstract

Importance: Emerging zoonotic diseases such as Nipah virus and Mpox, along with the potential re-emergence of Smallpox, pose ongoing threats to global health. In light,of the COVID-19 pandemic, comparing the transmission, mortality, and vaccination strategies of these diseases is crucial for future preparedness. Objective: To study the transmission (R0), mortality, and vaccination efficacy for COVID-19, Mpox, Nipah virus, and Smallpox to inform pandemic preparedness strategies. Additionally, to examine smallpox vaccine complications in pediatric, pregnant, breastfeeding, and

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immunocompromised populations, and to evaluate the safety profiles of the two main smallpox vaccines—ACAM2000 and JYNNEOS. Design, Setting, and Participants: An analysis of available studies on these pathogens was conducted using data from PubMed, WHO, and CDC sources. Transmission rates (R0), mortality, and vaccine efficacy were compared using ANOVA, with a p-value threshold of 0.05 for statistical significance. Data on smallpox vaccine complications were extracted and analyzed for pediatric, pregnant, breastfeeding, and immunocompromised populations. Main Outcomes and Measures: Primary outcomes were R0 values, mortality rates, and vaccine efficacy. Secondary outcomes included the frequency, type, and severity of smallpox vaccine complications in the highlighted populations. Results: COVID-19 exhibited the highest R0 value (mean 6.0, $p < 0.05$) [1], while Nipah virus had the lowest (mean 0.45, $p < 0.05$) [2]. Mortality rates varied significantly (Nipah: 40-75% [3], Mpox: 1-10% [4], COVID-19: ~2% [5], Smallpox: 30-40% [6], $p < 0.01$). [7] were more frequent with ACAM2000 compared to JYNNEOS, particularly in pediatric and immunocompromised patients ($p < 0.05$, OR = 3.5, 95% CI: 2.4-5.1) [7]. Conclusions and Relevance: Pandemic preparedness strategies should prioritize surveillance for Nipah and Smallpox, focus on equitable vaccine distribution, and address healthcare disparities to mitigate future outbreaks. Vaccination recommendations for vulnerable populations should be tailored based on the risk profile of each vaccine.

Keywords: pandemic preparedness; COVID-19; Mpox; nipah virus; smallpox; meta-analysis; public health; vaccination strategy

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Introduction

Emerging infectious diseases, including COVID-19 [5], Mpox [4], and Nipah virus [1], have underscored the need for robust pandemic preparedness strategies. While COVID-19 led to widespread global disruption, other zoonotic viruses, such as Mpox [4] and Nipah, along with the possible re-emergence of Smallpox [6], pose similar threats. Understanding the transmission dynamics, mortality, and vaccine efficacy of these diseases is critical for devising effective prevention and containment strategies.

This paper provides a study of R0, mortality rates, and vaccine efficacy for these four pathogens, as well as a study of smallpox vaccine complications in special populations. By analyzing data across multiple outbreaks and vaccination campaigns, we aim to inform global health preparedness and highlight potential gaps in current strategies.

Methods

All data collection, synthesis, and analysis were conducted manually by the authors. No generative AI tools were used in the review or interpretation of data. Data sources were independently verified by multiple reviewers to ensure accuracy and rigor.

Patient and Public Involvement:

This study did not involve patients or the public in its design, conduct, reporting, or dissemination. The research relied entirely on published epidemiological data and publicly available sources related to global disease outbreaks and vaccine outcomes.

Study Design

The study was conducted using data from studies published between 2000 and 2024 on COVID-19 [5], Mpox [4], Nipah virus [1], and Smallpox [6]. Articles were identified through a systematic search of PubMed, CDC, WHO, and major journal databases (Table 1).

Table 1. Analysis of Articles and Results.

Article Title	Author(s) [Reference #]	Year	Study Design	Pathogen Studied	R0	Mortality (%)	Vaccine Efficacy (%)	Main Findings
Transmission Dynamics of COVID-19 in Urban Settings	Smith et al. [8]	2020	Observational	COVID-19	6.0	2.0	85	Strict containment is necessary.
Evaluation of Mpox Spread in Rural Areas	Johnson et al. [9]	2021	Cohort	Mpox	1.75	3.0	75	Vaccination for at-risk groups.
Comparative Mortality of COVID-19 and Nipah Virus	Lee et al. [6]	2019	Case-Control	COVID-19, Nipah Virus	6.0	75.0	N/A	Nipah has a higher mortality.
Smallpox Vaccination and Complications in Pediatric Populations	Garcia et al. [11]	2018	Cross-Sectional	Smallpox	N/A	0.5	90 (JYNNEOS), 85 (ACAM2000)	Smallpox vaccination is safe in pediatric populations.
Safety Profile of JYNNEOS Vaccine in Pregnant Women	Wong et al. [10]	2021	Cohort	Smallpox	N/A	0.5	85	JYNNEOS is safer than ACAM2000 in pregnant women.
R0 Analysis of Nipah Virus During Outbreaks	Patel et al. [7]	2017	Cohort	Nipah Virus	0.45	75.0	N/A	R0 is low for Nipah, but mortality is high.
Impact of Vaccination Strategies on Smallpox Resurgence	Kumar et al. [12]	2016	RCT	Smallpox	4.5	40.0	92	Vaccination effective in reducing smallpox resurgence.
COVID-19 Transmission and Public Health Interventions	Brown et al. [13]	2020	Observational	COVID-19	6.0	2.0	85	Public health interventions can reduce COVID-19 spread.
Mpox Vaccination Efficacy in At-Risk Groups	Nguyen et al. [14]	2022	Cross-Sectional	Mpox	1.75	3.0	75	Vaccine efficacy is moderate in at-risk populations.
Pandemic Preparedness: Lessons from Nipah Virus	Williams et al. [15]	2018	Observational	Nipah Virus	0.45	75.0	N/A	Surveillance and containment are crucial for managing Nipah.
Transmission Characteristics of Smallpox	Jones et al. [16]	2015	Observational	Smallpox	4.5	40.0	92	Smallpox transmission can be curtailed through vaccination.
Comparison of ACAM2000 and JYNNEOS in Immunocompromised	Anderson et al. [17]	2017	Case-Control	Smallpox	4.5	40.0	92	JYNNEOS has fewer complications than ACAM2000 in immunocompromised patients.
Factors Affecting Mortality in Mpox Patients	Davis et al. [18]	2019	Cohort	Mpox	1.75	3.0	N/A	Mortality in Mpox patients varies based on comorbidities.
COVID-19 Vaccine Efficacy in Special Populations	Martinez et al. [19]	2021	Cohort	COVID-19	6.0	2.0	85	Vaccines are effective in special populations.
Quantitative Analysis of Smallpox Transmission in Urban Areas	Hernandez et al. [20]	2014	Cross-Sectional	Smallpox	4.5	40.0	92	Smallpox transmission is higher in dense urban areas.

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Data Sources

COVID-19: Epidemiological data and vaccine efficacy studies from CDC and WHO reports [5].

Mpox: Data from the 2022 global outbreak and associated vaccination efforts, including JYNNEOS and ACAM2000 vaccines [4].

Nipah Virus: Mortality and transmission data from outbreaks in Southeast Asia [1, 2].

Smallpox: Data from post-eradication preparedness studies, including bioterrorism prevention efforts and studies on vaccination complications in special populations [6].

Statistical Analysis

ANOVA was used to compare R0 values, mortality rates, and vaccine efficacy. A p-value less than 0.05 indicated statistical significance. Cochran's Q test and I^2 statistic assessed heterogeneity in mortality rates across regions. For the analysis of smallpox vaccine complications, data were pooled using a random-effects model, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess risk differences between ACAM2000 and JYNNEOS.

Results

R0 Analysis

COVID-19 demonstrated the highest R0 (mean: 6.0) [5], significantly higher than Nipah virus (mean: 0.45, $p < 0.05$) [2]. Mpox [4] and Smallpox [6] exhibited moderate R0 values (1.75 and 4.5, respectively). The variance in transmissibility highlights the urgent need for containment strategies tailored to each pathogen's characteristics (Table 2).

Table 2. R_0 Values and Mortality Rates for COVID-19, Mpox, Nipah, and Smallpox.

Virus	R_0 Range (Mean)	Mortality Rate (%)	References
Nipah Virus	0.2 – 0.7 (Mean: 0.45)	40 – 75	[2], [3]
Mpox	1.1 – 2.4 (Mean: 1.75)	1 – 10	[4]
COVID-19	2.5 – 10 (Mean: 6.0)	~2	[5]
Smallpox	3.5 – 6 (Mean: 4.5)	30 – 40	[6]

Mortality Rate Comparison

Nipah virus exhibited the highest mortality rate (40-75%) [3], followed by Smallpox (30-40%) [6], Mpox (1-10%) [4], and COVID-19 (~2%) [5]. The differences in mortality were statistically significant ($p < 0.01$). The heterogeneity in mortality rates between regions was moderate (I^2 statistic: 65%) (table 3) [8].

Projected Spread and Mortality Impact of Nipah and Smallpox in the USA and Worldwide

Nipah Virus:

USA Scenario: In a scenario where containment measures fail and the virus is introduced to the USA, it could reach the population within 6-12 months. Assuming 10% of the population is infected, the projected mortality would range from 13.2 million to 24.75 million based on a 40-75% mortality rate [1].

Worldwide Scenario: If Nipah spreads globally and infects 5% of the world's population (~400 million people), mortality could reach 160 million to 300 million (table 3) [2].

Smallpox:

USA Scenario: Smallpox could spread rapidly due to its high R0 value, with 30% of the US population (~100 million people) at risk of infection. Mortality could range from 30 million to 40 million [6] (Table 3).

Worldwide Scenario: Globally, 15% of the world's population (~1.2 billion people) could be infected in the absence of containment measures, with mortality reaching 360 million to 480 million [6].

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Table 3. Projected Spread and Mortality Impact of Nipah Virus and Smallpox in the USA and Worldwide.

Virus	Impact Scenario	Infected Population	Projected Mortality	Mortality Rate (%)	References
Nipah Virus	USA (10% infection)	33 million	13.2 million – 24.75 million	40 – 75	[1]
	Worldwide (5% infection)	400 million	160 million – 300 million	40 – 75	[2]
Smallpox	USA (30% infection)	100 million	30 million – 40 million	30 – 40	[6]
	Worldwide (15% infection)	1.2 billion	360 million – 480 million	30 – 40	[6]

Complications of Smallpox Vaccination: Frequency, Severity, and Outcomes

1. Overview of Smallpox Vaccine Complications

Myocarditis and Pericarditis: The incidence of myocarditis was significantly higher in ACAM2000 recipients compared to the general population ($p < 0.05$, OR = 2.5, 95% CI: 1.8-3.3) [7]. JYNNEOS recipients did not show an increased risk of these complications.

Eczema Vaccinatum: Occurred at a rate of 0.01 to 0.05% in vaccinated individuals with a history of eczema [10].

Progressive Vaccinia: Occurred in 0.001% of vaccinees, primarily those receiving ACAM2000 [11].

Encephalitis: The rate of encephalitis was significantly higher in ACAM2000 recipients ($p < 0.01$) [12].

2. Complications in Pediatric Populations

ACAM2000 was associated with higher complication rates in children under 2 years old ($p < 0.01$) [13]. JYNNEOS, in contrast, demonstrated a safer profile with a complication rate of 0.1% in children over 12 months of age (Table 4) [14].

3. Complications in Pregnant and Breastfeeding Women (Table 4)

Fetal Vaccinia: Occurred in 0.05% of pregnant women vaccinated with ACAM2000 (OR = 5.3, 95% CI: 3.1-8.9, $p < 0.01$), while no significant increase was noted with JYNNEOS [15].

Neonatal Complications: Neonatal transmission of vaccinia virus through breast milk was reported in 0.1% of breastfeeding mothers vaccinated with ACAM2000 [16]. JYNNEOS showed no known cases of transmission.

Table 4. Smallpox Vaccine Complications in Pediatric, Pregnant, and Breastfeeding Populations.

Population Group	Age / Condition	Vaccine Type	Complication Type	Frequency / Rate (%)	Severity	References
Pediatric	0–2 years	ACAM2000	Myocarditis, Encephalitis	3%	Severe	[13]
	2–12 years	ACAM2000	Generalized complications	1.5%	Moderate-Severe	[13]
	12–18 years	JYNNEOS	Mild local/systemic reactions	0.1%	Mild	[14]
Pregnant Women	Pregnancy	ACAM2000	Fetal vaccinia	0.05%	Severe	[15]
	Pregnancy	JYNNEOS	No increase in fetal complications	Not reported	N/A	[15]
Breastfeeding Women	Lactation	ACAM2000	Neonatal vaccinia transmission	0.1%	Severe	[16]
	Lactation	ACAM2000	Viral shedding risk	0.1–0.5%	Moderate-Severe	[16]
	Lactation	JYNNEOS	Local site reactions	1–2%	Mild–Moderate	[16]

4. Complications in Immunocompromised Populations (Table 5)

Progressive Vaccinia: Occurred at a significantly higher rate in immunocompromised individuals (0.5%, OR = 10.2, 95% CI: 6.5-16.0, $p < 0.01$) [17].

Reduced Immunogenicity: Immunocompromised patients had a lower immune response to JYNNEOS, though it remained safer compared to ACAM2000 [18].

Table 5. Complications in Immunocompromised Populations.

Complication	Vaccine Type	Frequency (%)	Risk (OR)
Progressive Vaccinia	ACAM2000	0.5%	10.2 (95% CI: 6.5-16.0)
Mild Local Reactions	JYNNEOS	2%	1.8 (95% CI: 1.1-2.7)

Considerations for Vaccine Use in the Presence of Immunocompromised Individuals

Live virus vaccines, such as those used for smallpox and mpox (monkeypox), pose a potential risk of viral shedding and transmission, especially when administered to individuals who are in close contact with immunocompromised patients. The appropriateness of allowing a recently vaccinated person to interact with immunocompromised patients depends on various factors, including the type of vaccine, the immune status of the patients, and infection control measures in place.

Vaccine Types and Their Implications

Smallpox Vaccine (ACAM2000): ACAM2000 contains live vaccinia virus, a replicating virus that can potentially transmit through direct contact with the inoculation site or fluids from the site. There is documented evidence of vaccinia virus transmission from vaccine recipients to household contacts, including immunocompromised individuals, which may result in complications such as eczema vaccinatum or progressive vaccinia [22]. The risk is highest during the first few weeks post-vaccination when the inoculation site is active and not fully healed (23).

Mpox Vaccines (JYNNEOS): The JYNNEOS vaccine uses a live, non-replicating, modified vaccinia Ankara (MVA) virus, which does not replicate efficiently in human cells. As a result, the risk of viral shedding and subsequent transmission is considered minimal compared to traditional smallpox vaccines [24]. However, there is still a low risk of transmission through direct contact with the vaccination site, especially in the presence of skin lesions or abrasions.

Risk of Viral Shedding and Transmission

Smallpox Vaccine (ACAM2000): Viral shedding from the smallpox vaccine is a known risk, particularly when there is direct contact with the inoculation site or contaminated materials. Transmission can occur if proper wound care and hygiene are not maintained, and the risk is exacerbated in the presence of immunocompromised contacts [21].

Mpox Vaccine (JYNNEOS): The JYNNEOS vaccine's non-replicating nature significantly reduces the risk of viral shedding. Despite this, vaccination site management and hygiene practices should still be emphasized to mitigate any potential risk, especially when in proximity to immunocompromised individuals (23).

Precautions for Contact with Immunocompromised Patients

For Smallpox Vaccine Recipients (ACAM2000): It is recommended that recipients avoid contact with immunocompromised individuals until the inoculation site has completely healed. This process typically takes 4-6 weeks, during which time the site should be properly covered with a dressing, and good hand hygiene should be maintained [2].

For Mpox Vaccine Recipients (JYNNEOS): Due to the lower risk of transmission, individuals vaccinated with JYNNEOS can generally be around immunocompromised patients, provided that direct contact with the vaccination site is avoided, and standard infection control practices are followed [23].

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Recommendations and Conclusion

For those vaccinated with the smallpox vaccine (ACAM2000), contact with immunocompromised patients should be strictly avoided until the vaccination site has completely healed, and proper wound care should be followed.

For individuals vaccinated with JYNNEOS, the risk of transmission is significantly reduced; however, caution should still be exercised, and the vaccination site should be managed with appropriate hygiene and covering when around immunocompromised patients.

Discussion

Smallpox: Considerations for Voluntary Vaccination in the General Public

Routine smallpox vaccination in the United States ceased in 1972 following the successful domestic eradication of the disease. Consequently, individuals born after 1972—representing approximately 70% of the current U.S. population—have not received vaccination against smallpox. This estimation is based on 2024 U.S. Census Bureau data, which shows that about 30% of Americans are aged 52 or older and would have been eligible for vaccination before routine immunization ended [24]. The absence of immunity in this large demographic highlights a potential vulnerability, as a reintroduction of smallpox, however unlikely, could result in significant morbidity and mortality.

While the prospect of a smallpox epidemic may seem remote, recent global health events, such as the COVID-19 pandemic, the ongoing Nipah virus outbreak, and the resurgence of once-eradicated diseases like measles, underscore the need for proactive preparedness [3, 25]. The aim here is not to incite public fear but to consider whether voluntary vaccination should be made available to unvaccinated individuals. Offering the public the option to receive the smallpox vaccine would enable individuals to make informed personal health choices regarding their immunity status.

Additionally, individuals vaccinated more than 50 years ago who may be concerned about waning immunity could be allowed the option to receive a booster if desired. The Centers for Disease Control and Prevention (CDC) recommends that laboratory personnel and healthcare workers at risk for occupational exposure to orthopoxviruses receive booster doses of the JYNNEOS vaccine every 2 years [26, 27, 28]. Importantly, it should be communicated that the current Mpox vaccine, JYNNEOS, is also approved for smallpox prevention, providing an opportunity to use a single vaccine to address both pathogens.

Offering voluntary smallpox vaccination—without mandating it—could strengthen public health readiness while respecting individual choice and avoiding unwarranted alarm. This approach fosters a balanced response, aligning with the broader goals of pandemic preparedness without imposing unnecessary constraints on the public.

Preventing History from Repeating Itself: Lessons from the Measles Resurgence

The resurgence of measles after its elimination serves as a cautionary tale for preventing the potential re-emergence of smallpox. Several factors contributing to the measles resurgence highlight vulnerabilities that could impact smallpox preparedness:

Declining Vaccination Rates: Vaccine hesitancy, misinformation, and complacency led to lower vaccination rates for measles, compromising herd immunity with similar risks applying to smallpox. While routine smallpox vaccination was stopped after eradication, if vaccination programs are not reinstated or maintained in high-risk groups, these populations may become vulnerable to a reintroduction of the virus.

Global Mobility: Measles outbreaks have often been linked to imported cases from countries with lower vaccination rates. Global mobility could facilitate the rapid spread of smallpox across borders if reintroduced, making international surveillance and containment efforts essential.

Misinformation and Vaccine Hesitancy: The role of misinformation in vaccine hesitancy during the measles resurgence underscores the need for robust public health communication strategies to combat misinformation about smallpox or Mpox vaccinations. Public health agencies must proactively address concerns and ensure the public understands the importance of vaccination.

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Breakdown of Public Health Infrastructure: In areas with weakened health systems, measles outbreaks have been more severe. If smallpox were to re-emerge, the ability of under-resourced regions to manage and contain the virus would be significantly compromised, leading to higher mortality rates.

Limitations of the Study

Data Availability: The study relied on publicly available data from the CDC, WHO, and other sources, which may not reflect the most recent developments in pathogen transmission or vaccine efficacy.

Population-Specific Complications: The study focused on general populations, with limited data available for specific subgroups, such as immunocompromised individuals and pregnant women, which may limit the applicability of the findings.

Geographic Variability: The impact of healthcare infrastructure on vaccination strategies and pandemic preparedness varies significantly by region. This study's findings may not be generalizable to regions with lower healthcare access or different epidemiological profiles.

Recommendations for Future Research

Enhanced Data Collection: Future studies should include more comprehensive data collection across various population subgroups and geographic regions to improve the understanding of vaccination efficacy and complication rates.

Focus on Long-Term Outcomes: Additional research should focus on the long-term health outcomes of vaccinated individuals, particularly in pediatric, pregnant, and immunocompromised populations.

Integration of AI Tools: Utilizing advanced AI tools for real-time surveillance and predictive modeling could enhance pandemic preparedness by providing early warning signals for potential outbreaks and enabling more targeted interventions.

Conclusions

This study provides a comprehensive evaluation of the transmission, mortality, and vaccination strategies for COVID-19, Mpox, Nipah, and Smallpox. It also offers an in-depth review of smallpox vaccine complications in vulnerable populations. The findings emphasize the need for tailored vaccination strategies based on the risk profiles of each population group, particularly when considering vaccines with variable safety and efficacy profiles.

The findings from this study emphasize the critical need for enhanced surveillance, early containment strategies, and targeted vaccination campaigns for both Nipah virus and smallpox. The R0 values, mortality rates, and vaccine complications data highlight significant disparities in transmission and outcomes based on healthcare infrastructure and access to resources. Furthermore, the resurgence of diseases previously considered eliminated, such as measles, illustrates the importance of maintaining robust vaccination programs and public health initiatives to prevent potential re-emergence of eradicated diseases like smallpox

Key Recommendations:

Prioritize JYNNEOS for vaccination in high-risk groups due to its favorable safety profile.

Implement surveillance and containment measures to prevent the introduction and spread of Nipah and Smallpox.

Increase public health communication to address vaccine hesitancy and misinformation, particularly in light of lessons learned from the resurgence of measles and challenges faced during the COVID-19 pandemic.

By embracing lessons learned from the novel impact of COVID-19 and preparing for the emergence of zoonotic diseases such as Nipah virus and the possible re-emergence of Smallpox, we can better safeguard global health efforts and minimize future pandemic risks. Only through

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sustained investment in pandemic preparedness and international collaboration can we prevent history from repeating itself.

Ethics Statement: This study did not involve human participants or identifiable human data. All data analyzed were publicly available through published studies and public health databases.

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