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Original Article

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Exploring the impact of vaccination coverage on yellow fever incidence: a country-level analysis of lagged effects in South America (2015–2023)

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ABSTRACT

Background: Yellow fever (YF) remains a significant public health concern in South America, particularly in Brazil, Colombia, Ecuador, and Peru. Vaccination campaigns are essential for controlling disease transmission, but their effects may vary due to differences in coverage, healthcare systems, and surveillance. Understanding lagged effects—how vaccination in one-year influences cases in the next—can guide more effective strategies.
Methods: We conducted a secondary data analysis using World Health Organization data from 2015 to 2023. Annual vaccination coverage (%) and confirmed YF cases were extracted for Brazil, Colombia, Ecuador, and Peru. Vaccination coverage values were shifted forward by one year to assess lagged effects. Pearson's correlation coefficient was calculated for each country, with significance set at $P < 0.05$. Analyses were performed in R (v4.3).
Results: From 2015 to 2023, Brazil reported the highest total number of cases (n = 2,278), followed by Peru (n = 163), Colombia (n = 9), and Ecuador (n = 3). Vaccination coverage ranged from 43.2%–99.2% (Brazil), 54.3%–90.0% (Colombia), 69.8%–96.2% (Ecuador), and 50.2%–75.0% (Peru). Overall correlation between coverage and cases was r = –0.32 (p = 0.058). Lagged correlation analysis showed significant associations for Colombia ($r = -0.917$, $P = 0.001$) and Ecuador ($r = 0.722$, $P = 0.043$), but not for Brazil ($r = -0.550$, $P = 0.158$) or Peru ($r = 0.051$, $P = 0.905$).
Conclusion: Lagged correlation analysis suggests that vaccination effects on YF incidence vary by country. Sustained coverage appears most protective in Colombia, while results in Ecuador highlight possible surveillance or reporting challenges. Tailored strategies and improved data systems are needed to optimize YF control.

Keywords: Yellow fever; Vaccination coverage; South America; Time factors; Disease outbreaks

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Bravo Loaiza SI, Kang S, Jeong HJ; Data curation: Bravo Loaiza SI; Formal analysis: Bravo Loaiza SI; Methodology: Bravo Loaiza SI, Kang S; Software: Bravo Loaiza SI; Validation: Kang S, Jeong HJ; Investigation: Bravo Loaiza SI; Writing - original draft: Bravo Loaiza SI, Jimenez Baez DI, Santos Alfaro NV, Mogrovejo Coronel AP, Escobar Arévalo DA; Writing - review & editing: Kang S, Jeong HJ.

INTRODUCTION

Yellow fever (YF) is a re-emerging, life-threatening viral hemorrhagic disease caused by a flavivirus transmitted primarily by *Aedes* and *Haemagogus* mosquitoes. Despite the availability of a highly effective vaccine, YF continues to cause sporadic outbreaks, particularly in tropical regions of Africa and South America. In recent years, the resurgence of YF in urban centers, increased international travel, and gaps in immunization coverage have raised global concern about the potential for large-scale epidemics.[1,2]

Historical estimates of global YF vaccination coverage from 1970 to 2016 reveal significant gaps across endemic regions, reinforcing the importance of sustained immunization efforts.[3] In 2016–2017, Angola and the Democratic Republic of the Congo experienced a major YF outbreak, resulting in over 7,000 suspected cases and hundreds of deaths.[4,5] The outbreak underscored the urgent need for timely surveillance, rapid case detection, and understanding of factors influencing disease severity and hospitalization. While previous studies have focused on vaccination coverage and vector control efforts during this outbreak, limited data exist on clinical and demographic predictors of severe outcomes among suspected YF cases in this context.[6]

In recent years, countries including Brazil, Colombia, Peru, and Ecuador have reported sporadic yet significant resurgences of YF cases.[7] These outbreaks often follow declines in population-level vaccination coverage or lapses in routine immunization programs, underscoring the fragility of regional control efforts.[8] The World Health Organization (WHO) and the Pan American Health Organization have emphasized the importance of sustained high vaccination coverage to prevent reemergence in both urban and sylvatic transmission cycles.[7]

The 4 included countries differ in immunization delivery models, where Colombia and Ecuador maintain stronger routine preventive vaccination systems, while Brazil and Peru have historically relied more on reactive campaign-based immunization, which may result in heterogeneous temporal trends.[7]

Although several descriptive and epidemiological reports have documented YF activity in South America, there is limited regional analysis examining the temporal association between national vaccination efforts and disease outcomes.[3] There is a lack of empirical research exploring how changes in annual vaccination coverage may influence case numbers in subsequent years. Understanding this lagged effect is essential for informing timely public health action, optimizing vaccination strategies, and predicting potential outbreak scenarios.

Vaccination effects on population-level disease outcomes may not be immediate. First-dose immunity against YF develops approximately 10 days post-vaccination, and full population-level impact depends on gradual accumulation of herd immunity and immunization coverage over time.[9] In addition, surveillance and reporting delays, ecological transmission cycles, and seasonal vector dynamics may shift observable disease reduction into subsequent years.[10] Therefore, exploring lagged associations provides a more realistic view of vaccination impact beyond same-year comparisons.

This study aimed to investigate the relationship between YF vaccination coverage and disease incidence across 4 South American countries—Brazil, Colombia, Ecuador, and Peru—over the period 2015 to 2023. By analyzing lagged correlations between coverage and cases using

WHO-reported data, this research provides insight into the delayed impact of vaccination programs and highlights the need for sustained immunization efforts in preventing YF resurgence in the region.

Research question: Does national YF vaccination coverage in year t associate with YF incidence in year t+1 across Brazil, Colombia, Ecuador, and Peru?

Hypothesis: Higher vaccination coverage at year t is associated with lower YF incidence at t+1, acknowledging possible heterogeneity by country due to surveillance, campaign timing, and outbreak dynamics.

METHODS

To address the research question, this study investigates the lagged relationship between YF vaccination coverage and subsequent incidence in Brazil, Colombia, Ecuador, and Peru between 2015 and 2023. By focusing on a one-year lag, the analysis aims to capture the delayed effect of immunization campaigns on disease outcomes, while acknowledging that different lag intervals may also influence results. We hypothesize that increased vaccination coverage in a given year is associated with reduced YF incidence in the following year, particularly in countries with stronger routine immunization and outbreak response systems.

While the primary analysis used a 1-year lag to reflect the expected timeframe of population-level effects from vaccination campaigns, sensitivity analyses were performed using 0- and 0-year lags. This allowed us to evaluate whether immediate or more delayed associations were present.

At the same time, we anticipate that in countries with lower incidence or inconsistent surveillance, such as Ecuador and Peru, the relationship may be weaker or even counterintuitive. This approach seeks to generate insights into the country-specific effectiveness of vaccination efforts and highlight areas where additional strategies may be required.

Study design and data sources

This study used an ecological design, drawing on publicly available secondary data. Annual confirmed YF case counts, and vaccination coverage estimates for Brazil, Colombia, Ecuador, and Peru were obtained from the WHO database for the period 2015–2023. Vaccination coverage was measured as the percentage of the target population immunized against YF, reported separately by national governments and validated by WHO.

YF incidence was analyzed using annual confirmed case counts (raw numbers), as standardized population-denominator data were not consistently available across all years and countries for reliable incidence rate computation. This limitation is acknowledged in the discussion.

Statistical analysis

Descriptive analyses were performed to summarize case counts and vaccination coverage across countries and over time. Pearson's product–moment correlation coefficient was applied to assess the association between vaccination coverage in a given year and YF incidence in the following year (lagged correlation). Correlations were calculated both overall and stratified by country, with corresponding 95% confidence intervals and *P*-values. A significance level of

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$P < 0.05$ was considered statistically significant. Analyses were conducted using R statistical software (version 4.3; R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

This study relied exclusively on secondary, publicly available data from the WHO and did not involve human participants, patient-level data, or animals. As such, institutional review board approval and informed consent were not required.

RESULTS

Between 2015 and 2023, a total of 2,453 confirmed cases of YF were reported across the 4 countries included in the analysis (**Fig. 1**). Brazil accounted for the majority of cases (n = 2,278), followed by Peru (n = 163), Colombia (n = 9), and Ecuador (n = 3). The mean annual number of cases was highest in Brazil (mean, 253.1; standard deviation [SD], 473.0), followed by Peru (mean, 18.1; SD, 18.3), Colombia (mean, 1.0; SD, 2.0), and Ecuador (mean, 0.3; SD, 1.0) (**Table 1**).

Vaccination coverage varied over time and between countries. Ecuador had the highest average coverage (mean, 82.5%; SD, 9.5%), followed by Colombia (mean, 80.8%; SD, 11.1%), Brazil (mean, 61.1%; SD, 16.5%), and Peru (mean, 61.0%; SD, 7.6%). Coverage ranges were broad, with Brazil ranging from 43.2% to 99.2%, Colombia from 54.3% to 90%, Ecuador from 69.8% to 96.2%, and Peru from 50.2% to 75.0%.

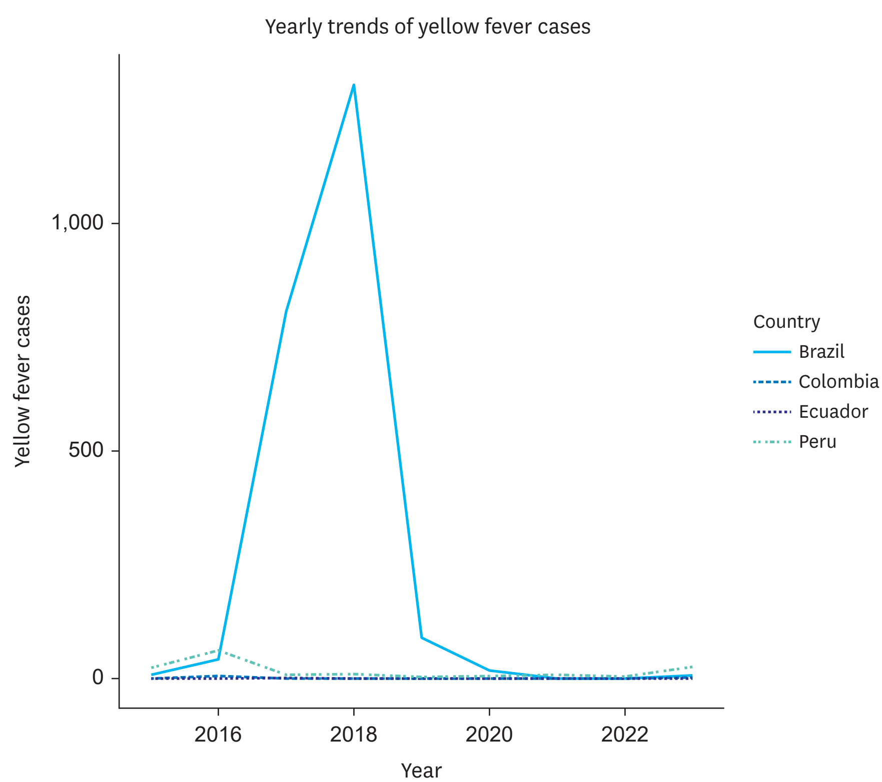

Fig. 1. Annual yellow fever cases by country (2015–2023). Yearly reported yellow fever cases in Brazil, Colombia, Ecuador, and Peru. Brazil shows marked peaks in 2017–2018, while other countries maintain relatively low incidence levels with occasional spikes.

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Table 1. Descriptive statistics for yellow fever cases and vaccination coverage

Country	Mean cases per year	SD of cases	Total cases	Mean vaccination coverage (%)	SD of coverage
Brazil	253.0	473.0	2,278	61.1	16.5
Colombia	1.0	2.0	9	80.8	11.1
Ecuador	0.3	1.0	3	82.5	9.5
Peru	18.1	18.3	163	61.0	7.63

Table 1 summarizes the key descriptive statistics (mean, SD, total cases, etc.) for yellow fever cases and vaccination coverage in each country from 2015 to 2023.
SD = standard deviation.

The lagged correlation analysis, comparing vaccination coverage in a given year with YF incidence in the subsequent year, showed country-specific patterns (**Table 2**). Colombia demonstrated a strong and statistically significant negative correlation ($r = -0.917$, $P = 0.001$; 95% confidence interval [CI], −0.985 to −0.600), while Ecuador exhibited a significant positive correlation ($r = 0.722$, $P = 0.043$; 95% CI, 0.034 to 0.945). Brazil had a moderate but non-significant negative correlation ($r = -0.550$, $P = 0.158$; 95% CI, −0.904 to 0.253), and Peru showed no meaningful association ($r = 0.051$, $P = 0.905$; 95% CI, −0.678 to 0.729) (**Fig. 2**).

To enhance cross-country comparison, we generated a summary visualization of lag-1 correlation coefficients (**Fig. 3**). This bar chart highlights the marked heterogeneity across

Table 2. Lagged correlation between vaccination coverage and yellow fever cases by country

Country	Lagged correlation estimate	*P*-value	95% confidence interval
Brazil	−0.550	0.158	−0.904, 0.253
Colombia	−0.917	0.00134	−0.985, −0.600
Ecuador	0.722	0.0433	0.0344, 0.945
Peru	0.0509	0.905	−0.678, 0.729

Table 2 presents the results of the lagged correlation analysis between vaccination coverage and yellow fever cases for each country. Significant correlations ($P < 0.05$) are highlighted, showing the potential delayed impact of vaccination efforts on yellow fever case numbers.

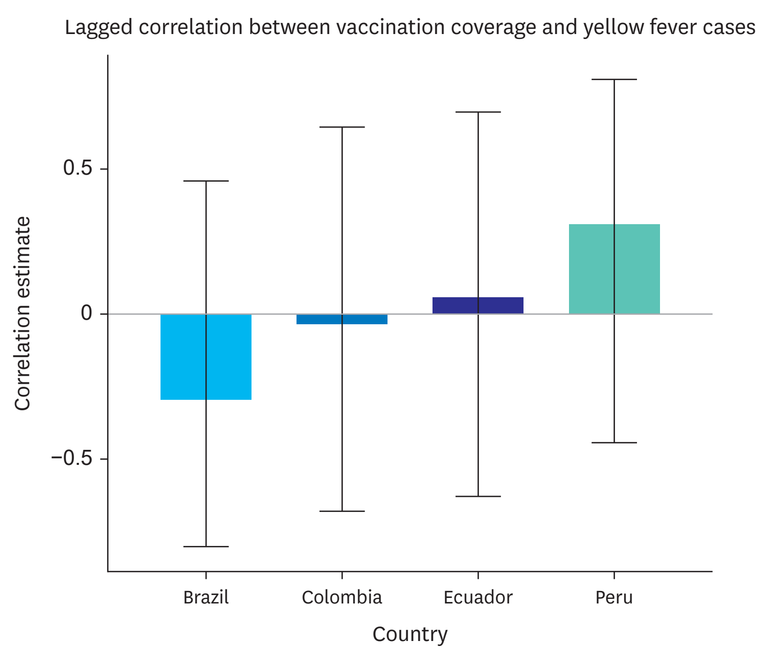

Fig. 2. Lagged correlation by country (vaccination impact). Visual representation of lagged correlation coefficients (vaccination coverage in year *t* vs. cases in year *t+1*) for Brazil, Colombia, Ecuador, and Peru, highlighting significant inverse correlation in Colombia and significant positive correlation in Ecuador.

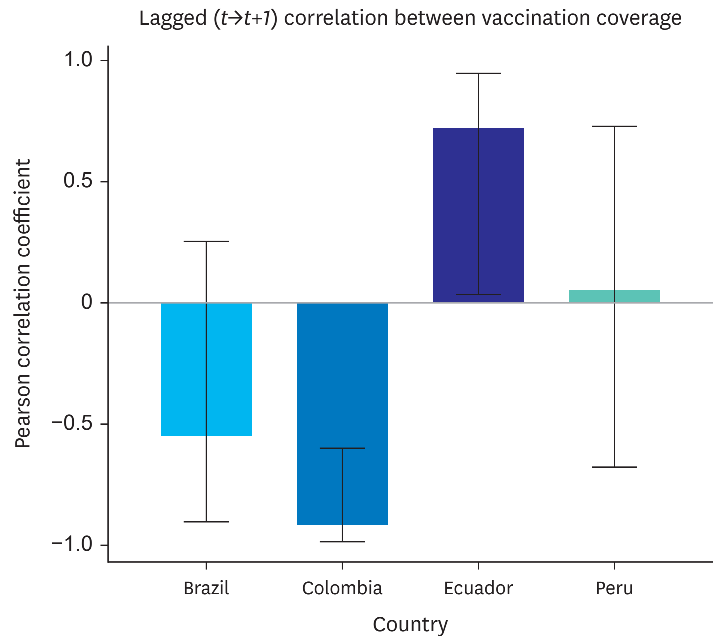

Fig. 3. Lagged (*t*→*t*+*1*) correlation between vaccination coverage and yellow fever incidence by country. Bar chart showing Pearson correlation coefficients for the 1-year lag across the 4 study countries. Error bars indicate 95% confidence intervals. Colombia exhibits a strong inverse correlation, Ecuador shows a significant positive correlation, and both Brazil and Peru display non-significant associations.

countries: Colombia demonstrates a strong and statistically significant inverse association between vaccination coverage and next-year incidence, whereas Ecuador shows a significant positive association. Brazil displays a moderate but non-significant negative correlation, while Peru's estimate remains close to zero with wide confidence intervals. This visual representation reinforces the country-specific variability observed in the numerical results.

Sensitivity analyses with same-year (lag 0) and 2-year (lag 2) correlations showed no statistically significant associations across any country (**Supplementary Tables 1** and **2**). These findings support the one-year lag as the most informative interval for evaluating the relationship between vaccination coverage and YF incidence during the study period (**Supplementary Fig. 1**).

The year with the highest number of reported cases for each country was: Brazil in 2018 (1,307 cases), Colombia in 2016 (6 cases), Ecuador in 2017 (3 cases), and Peru in 2016 (62 cases). These asynchronous outbreak peaks highlight the varied epidemiologic patterns of YF across the study countries (**Fig. 4**).

Negative binomial regression (**Table 3**) indicated that vaccination coverage was associated with a reduction in YF cases (incidence rate ratio [IRR] per 1% increase = 0.96; 95% CI, 0.90–1.05; $P = 0.13$), although this result did not reach statistical significance. Country effects were pronounced: compared to Brazil, Colombia (IRR, 0.012; $P < 0.001$), Ecuador (IRR, 0.004; $P < 0.001$), and Peru (IRR, 0.104; $P = 0.003$) exhibited markedly fewer expected cases.

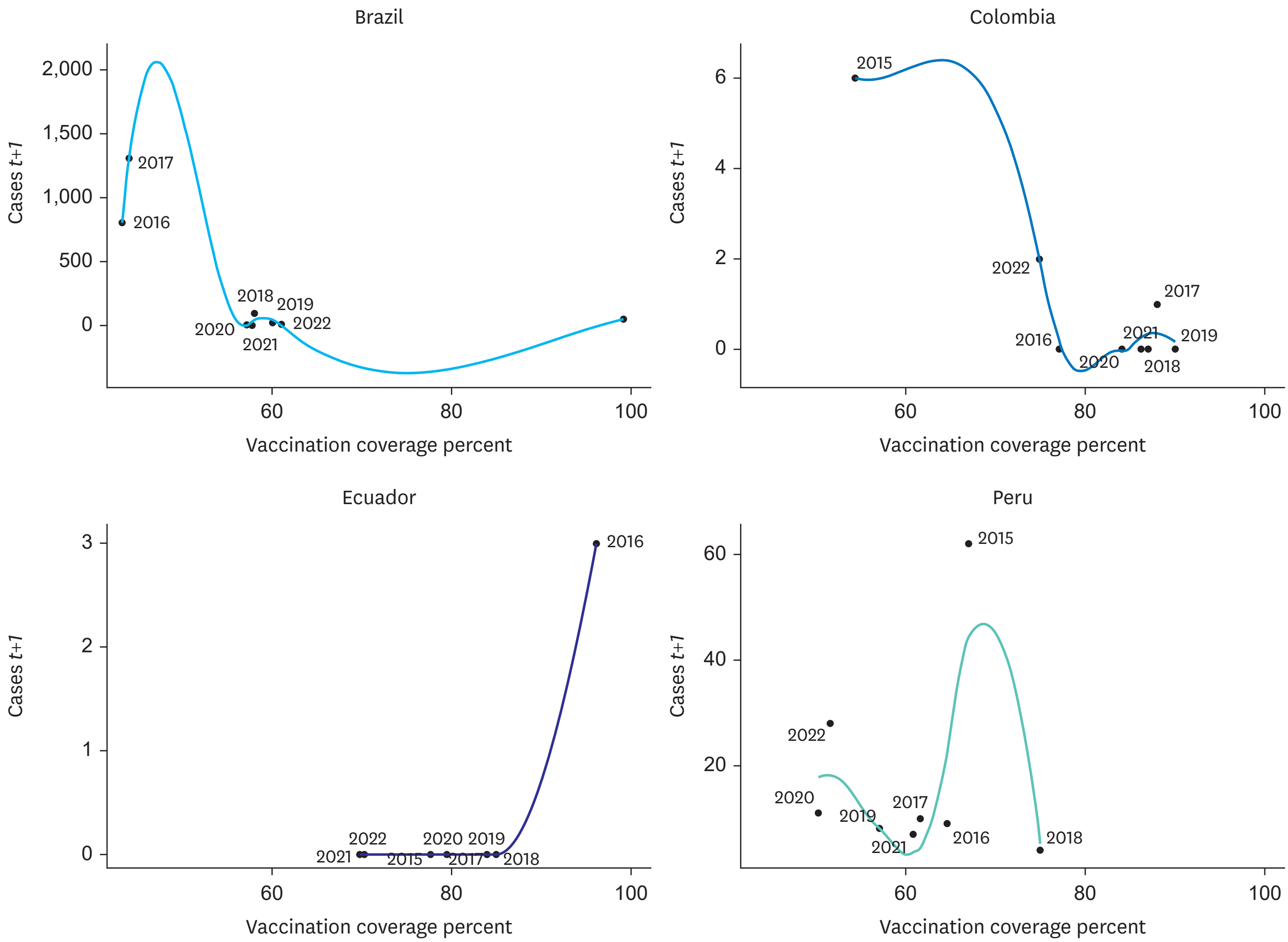

Fig. 4. Country-wise scatterplots of vaccination coverage at year *t* vs. yellow fever cases at year *t+1*. Scatterplots for Brazil, Colombia, Ecuador, and Peru (2015–2023) showing vaccination coverage in year *t* against yellow fever cases in year *t+1*. LOESS smoothing curves illustrate trends, and year labels highlight temporal variation. The plots demonstrate strong inverse lagged associations in Colombia, a positive relationship in Ecuador, and weaker or inconsistent associations in Brazil and Peru.

Table 3. Negative binomial regression of yellow fever cases and vaccination coverage (2015–2023)

Variable	IRR	95% CI (Lower–Upper)	*P*-value
Vaccination coverage (%)	0.96	0.90–1.05	0.129
Colombia (vs. Brazil)	0.012	0.0006–0.128	< 0.001
Ecuador (vs. Brazil)	0.004	0.0002–0.060	< 0.001
Peru (vs. Brazil)	0.104	0.018–0.562	0.003

This table presents the IRRs and 95% CIs from the negative binomial regression analysis of yellow fever cases (2015–2023). The model included vaccination coverage (per 1% increase) and country indicators, with Brazil as the reference category. IRRs below 1 indicate reduced expected case counts, while IRRs above 1 indicate increased expected case counts.
IRR = incidence rate ratio; CI = confidence interval.

DISCUSSION

This study examined the lagged association between YF vaccination coverage and reported YF incidence across 4 South American countries—Brazil, Colombia, Ecuador, and Peru—using national surveillance data from 2015 to 2023. Burden modelling across Africa and Latin

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America suggests strong heterogeneity in incidence, which reminds us to interpret national-level associations cautiously given subnational variation.[11] Modeling studies emphasize the sensitivity of YF burden estimates to assumptions about vaccination effectiveness and reporting completeness.[12]

The results indicate that Colombia exhibited a strong and statistically significant inverse association, with higher vaccination coverage linked to lower case counts in the following year. In contrast, Ecuador showed a significant positive correlation, where higher coverage in one year was associated with increased reported cases in the subsequent year. For Brazil and Peru, no statistically significant lagged associations were detected, making it difficult to draw firm conclusions about the relationship between coverage and incidence in these contexts.

Previous studies have demonstrated that high population coverage confers herd immunity and substantially lowers transmission risk.[7,13] Colombia's consistent vaccination programs, experience with outbreak control, and integration of routine and reactive campaigns may have contributed to this observed effect.[13] The positive correlation in Ecuador, however, contrasts with expectations. This pattern could reflect the impact of reactive vaccination campaigns conducted in response to outbreaks, whereby coverage increases occur after heightened transmission, thus creating a temporal sequence where elevated coverage precedes higher incidence.[1,5] It may also be influenced by underreporting in low-incidence years, localized outbreaks in high-risk zones, or delays in detection despite high coverage.

For Brazil and Peru, the absence of significant findings may result from a combination of factors, including fluctuations in annual coverage, asynchronous outbreak peaks, variability in vector ecology, and limitations in national-level analyses that may mask subnational patterns.[14] In Brazil, large outbreaks such as those in 2017–2018 could have disrupted straightforward trends, while in Peru, coverage expansion has been modest, potentially limiting measurable impact within the timeframe studied.[15]

Our sensitivity analyses confirmed that neither same-year (lag 0) nor 2-year (lag 2) correlations demonstrated meaningful associations between vaccination coverage and YF cases. This strengthens the rationale for using a 1-year lag, which yielded interpretable patterns in Colombia and Ecuador. While this analysis applied a 1-year lag to capture the likely temporal impact of immunization, the effects of vaccination on outbreak risk may be non-linear or longer-term, particularly in regions with fluctuating vector populations or environmental drivers.[16] The use of simple Pearson correlations offers exploratory insight but does not adjust for potential confounders such as climate, mobility, and vector control measures. Future research using distributed lag models or multivariable approaches could improve causal inference and account for these factors.

Vaccine failure may also contribute to the limited impact of coverage increases. Primary failure refers to a lack of immune response after vaccination, while secondary failure involves waning immunity over time. Both vaccine-related factors (vaccine attenuation and regimes) and host-related factors (host genetics, immune status, age, health, and nutritional status) can be involved.[17] Considering these limitations, some authors argue that expanding vaccine use and enforcing the International Health Regulations is essential, particularly since the emergence of imported cases may not only reflect individual-level vaccine failure but also systemic shortcomings in requiring vaccination for travelers to areas with active transmission.[18]

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Moreover, as highlighted by recent vaccine introductions such as the R21 malaria vaccine in Africa, robust post-vaccination surveillance systems are critical to monitor long-term effectiveness, identify potential declines in immunity, and detect early signs of breakthrough infections. Continuous pharmacovigilance and integration of vaccination and disease surveillance data can help differentiate true vaccine failure from gaps in program implementation or reporting systems.[19]

These findings are biologically plausible given that YF vaccine-derived immunity develops rapidly but may take time to produce visible epidemiologic effects, especially at the population level.[9] YF transmission is also influenced by sylvatic and peri-urban cycles, climatic seasonality, and vector population fluctuations, which can delay measurable reductions in disease burden following vaccination scale-up.[3]

Despite these limitations, the findings emphasize that vaccination coverage alone does not uniformly predict reduced YF incidence at the national level. In Colombia, sustained high coverage appears to confer delayed protective effects, while in Ecuador, further investigation is needed to clarify the counterintuitive relationship. Strengthening subnational surveillance, tailoring outbreak response, and coordinating cross-border vaccination efforts remain critical to sustaining YF control in South America.[20]

Countries with weaker health systems may underreport YF cases and struggle with vaccination coverage. This aligns with Lee and Lee[21] in their study "Association between health systems and universal health coverage and COVID-19 testing rates in 194 countries," which showed that stronger health systems and broader universal health coverage lead to better disease detection and response. Also, misclassification of vaccination status is a recognized issue in seroepidemiologic studies; for instance, Tran and Perkins[22] demonstrated how self-report or administrative records may diverge from serological evidence, which can bias estimates of vaccine impact. Strengthening health systems, investing in the workforce, and improving access and quality are essential for sustainable YF control.

Understanding delayed vaccination effects is crucial for timing preventive and reactive vaccination strategies, evaluating campaign success, and forecasting outbreak risk. Future analyses incorporating population denominators, ecological indicators, and vector seasonality could better characterize these temporal mechanisms.

This study examined the temporal relationship between YF vaccination coverage and subsequent incidence in Brazil, Colombia, Ecuador, and Peru from 2015 to 2023. The findings suggest a strong and statistically significant inverse association in Colombia, consistent with the protective effect of vaccination programs over time. In contrast, Ecuador showed a statistically significant but unexpected positive association, likely reflecting sparse case counts, underreporting, or other contextual factors. Brazil and Peru demonstrated no clear lagged correlation, underscoring the complexity of outbreak-driven dynamics and the limitations of national-level analyses.

The negative binomial regression supported these trends, showing that higher vaccination coverage was associated with fewer cases overall, though this effect did not reach statistical significance across all countries. Brazil accounted for most regional cases, while Colombia, Ecuador, and Peru reported substantially fewer, emphasizing the heterogeneous epidemiology of YF across South America.

These results highlight that the impact of vaccination may not be immediate or uniform across settings, and that surveillance quality, outbreak patterns, and campaign implementation strongly influence observed outcomes. Maintaining high routine vaccination coverage remains essential, but targeted approaches are needed to address subnational gaps and populations at increased risk.

Future research should explore finer-scale data, incorporate ecological and demographic covariates, and apply more advanced modeling approaches, including time-series and regression-based analyses, to better capture the delayed and nonlinear effects of vaccination. Strengthening regional collaboration in immunization and surveillance will be key to mitigating future outbreaks and sustaining progress against YF.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Same-year (lag 0) correlation between vaccination coverage and yellow fever cases by country

Supplementary Table 2

Two-year (lag 2) correlation between vaccination coverage and yellow fever cases by country

Supplementary Fig. 1

Vaccination coverage vs. yellow fever cases (2015–2023). Scatter plots illustrating the relationship between annual vaccination coverage (%) and yellow fever incidence for each country. Patterns suggest varying associations, with no uniform trend across all settings.

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