Evaluating progress towards the elimination of hepatitis B in children in Colombia: a two-phase study

Background

Global health sector strategy on viral hepatitis includes target to reduce the prevalence of chronic HBV infection in children to ≤ 1% by the year 2020, and to ≤ 0.1% by 2030 (WHA, May 2016)

- PAHO goal: ≤ 0.1% in children aged 5 years by 2020
- WPRO goal: ≤ 0.1% in children by 2030
- EURO goal: ≤ 0.5% HBsAg in vaccinated cohorts
- Previously established targets in WPRO, EMRO, and AFRO: 1% or 2%

Methods needed to verify achievement of target

- To date, have used representative national serosurveys
- But measuring new low targets would require very large sample sizes
  - To measure 1% +/- 0.5% approx. 1550 children
  - To measure 0.1% +/- 0.05 approx. 20,000 children

Background

Similar issue addressed for MNTE

- Target: 1/1000 births
- Two phase approach:
  - Risk assessment to identify areas of highest risk
  - Community based surveys in those areas (using LQAS methods) to identify NT deaths
- Rationale: If areas of highest risk are shown to meet target, then lower risk areas will also have met the goal.

Can a similar type of approach be used for hep B verification?

- Risk assessment: What types of data are needed and are they available to the level of detail required? How precisely and how accurately can different strata of risk be distinguished.
- Verification survey: What is the minimum area to be surveyed? Use of 'classification cluster survey' methods as alternative to LQAS.

Objectives

Pilot a 2 phase method for evaluating low levels of HBV prevalence in the context of verifying the achievement of HBV elimination targets.

- Phase 1: Rank areas by risk using existing geographically detailed data relevant to hepB
- Phase 2: Targeted classification serosurvey in high risk areas to assess likelihood that prevalence is greater than/less than 0.1%

¿Why Colombia?

- Coverage with hepB3 and hepB-BD in 2015 was 91% and 87% respectively, with similar coverage levels over the past decade.
- Serosurvey in Colombian Amazon in 1999 (de la Hoz, 2008)
  - Previously high rates of HBV compared to rest of country
  - 72% decline in prevalence of antiHBc among children compared to 1992
  - Prevalence of chronic infection in children 6-7 years 0.3% vs. 3% in children 8-11 years
- Availability of geographically detailed data for risk assessment.

Phase 1: Risk assessment

Analysis of existing data – Main indicators used

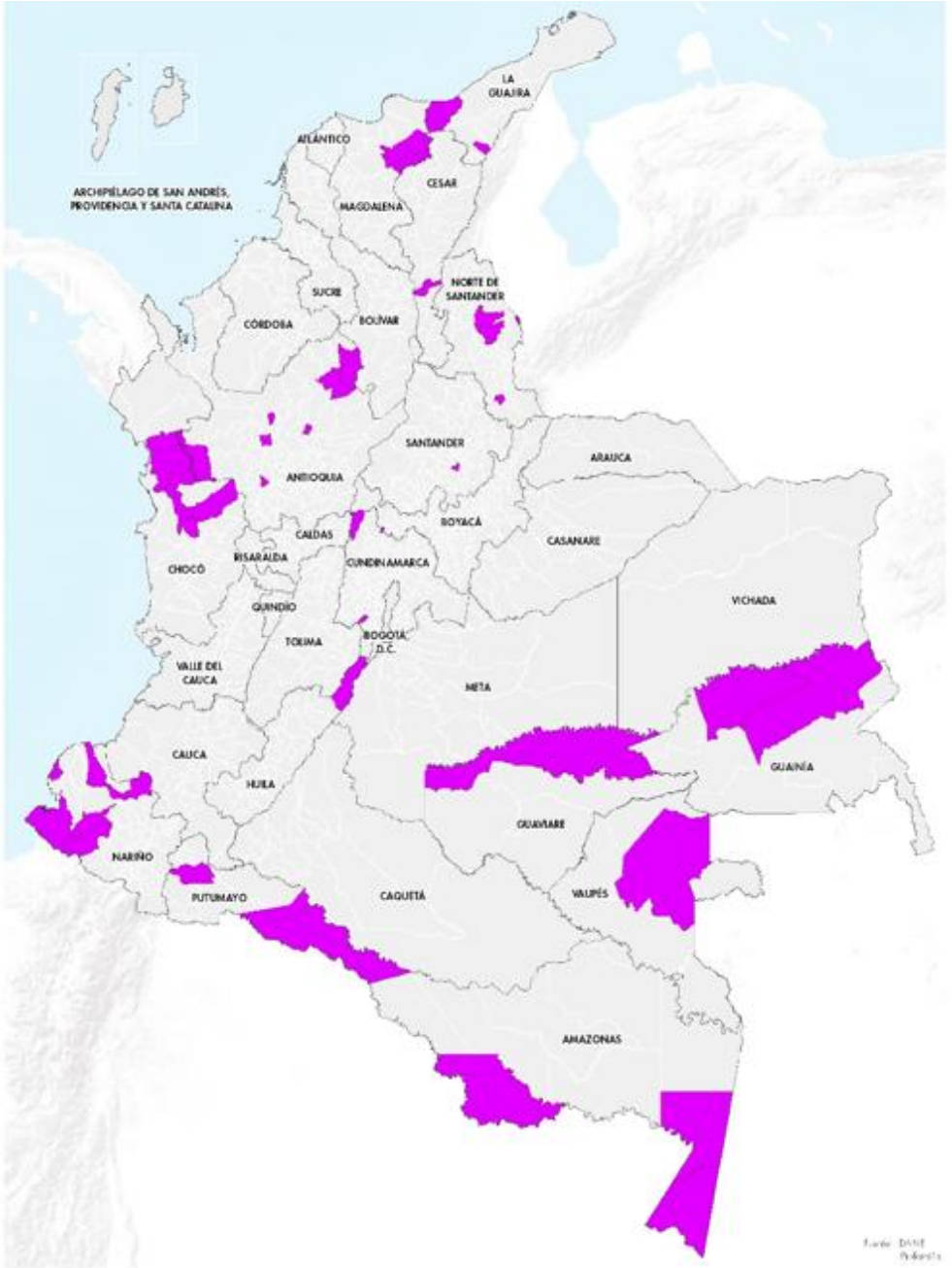
- Cases of HBV infection in pregnant women (per 1,000 population) via national surveillance - 2008-2013.
- Institutional delivery rates – 2008-2013
- Immunization coverage data: HepB3 – 2008-2013
- Previous serologic studies

→Used municipality level data (except serologic studies)

→Other evaluated data that were not used: Immunization coverage data –Hep B BD; Blood bank testing data (HBsAg+) and antenatal screening.

Results of Phase 1:

- **36 municipalities identified** covering a population of approx. 1 million persons (including 137K children 5-10 years)
  - Some excluded based on security and replaced by next highest.
  - Included 11 departments previously identified by serologic studies plus additional 4 departments



Phase 2: Serosurvey

Population-based household survey
- 36 ‘high risk’ municipalities
- Enrollment of children 5-10 years.
- Multistage probability sampling (EA, segment and child)

Powered for ‘classification’*
- Useful when objective to classify prevalence as being above or below a certain level
  - Smaller sample sizes than when aim to provide a precise estimate of prevalence.
- HO: HBsAg prevalence ≤ 0.001 VS. HA: HBsAg prevalence> 0.001 (alternative prevalence = 0.004)

Testing for HBsAg by rapid test (bioMerieux Vikia™)
- WHO pre-qualified

Collection of additional information by questionnaire
- Basic demographic data
- Immunization history – Vaccination cards or oral report
- Access to health care services

*World Health Organization Vaccination Cluster Surveys: Reference Manual (WHO, 2018)

Phase 2 Results

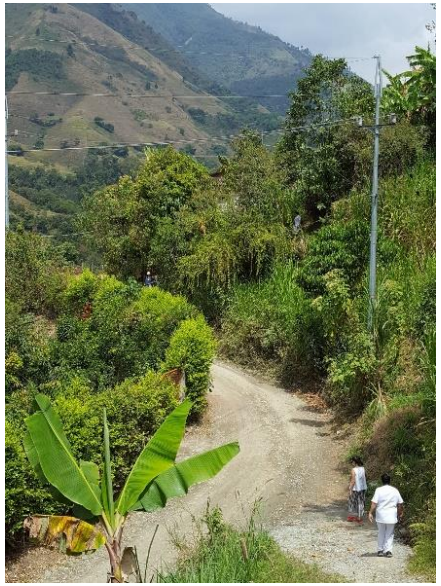
Implemented by Profamilia

35 of 36 targeted municipalities

94% participation in the survey.

3,203 enrolled children

- 45.2% Afrocolombian, 14.3% Indigenous, 40.5% other
- 77.6% covered by subsidized public health insurance, 14.4% with self-paid insurance and 5% not covered by social security system
- 88.2% were born in health facilities, 11.4% at home
- Nearly 100% enrolled in school
- 90% reported having vaccination cards (52% available at time of survey)



Phase 2 Results

- No infections (0/3,203)
  - **95% Upper confidence limit <0.1%** (0.09% Exact, 0.08% Wilson)
- High immunization coverage (card confirmed or oral report)
  - **96.1%** (95.1-97.1%) hepB3 and **94.5%** (93.3- 95.7%) hepB BD
- Lower BD coverage in children who were:
  - Born at home **78.8%** (72.5% - 85.1%)
  - Indigenous **86.6%** (80.7% - 92.4%)
  - Foreign born **78.2%** (63.8% - 92.6%)
  - Not covered by social security **90.8%** (81.7% - 99.8%)
- Also, despite high BD coverage, not always timely
  - Among those w/ card confirmed hepB BD, **26.6%** were vaccinated more than 2 days after birth, including 18.8% vaccinated 7+ days after birth

Hepatitis B investment case for Colombia

Objectives

To determine the most cost-effective and affordable scenarios to achieve elimination goals for hepatitis B by 2030.

Methods

The PROGReSs model was used to estimate incident cases, prevalence and health and economic outcomes of prevention, diagnosis and treatment scenarios, based on the hepatitis B information collected through different sources.

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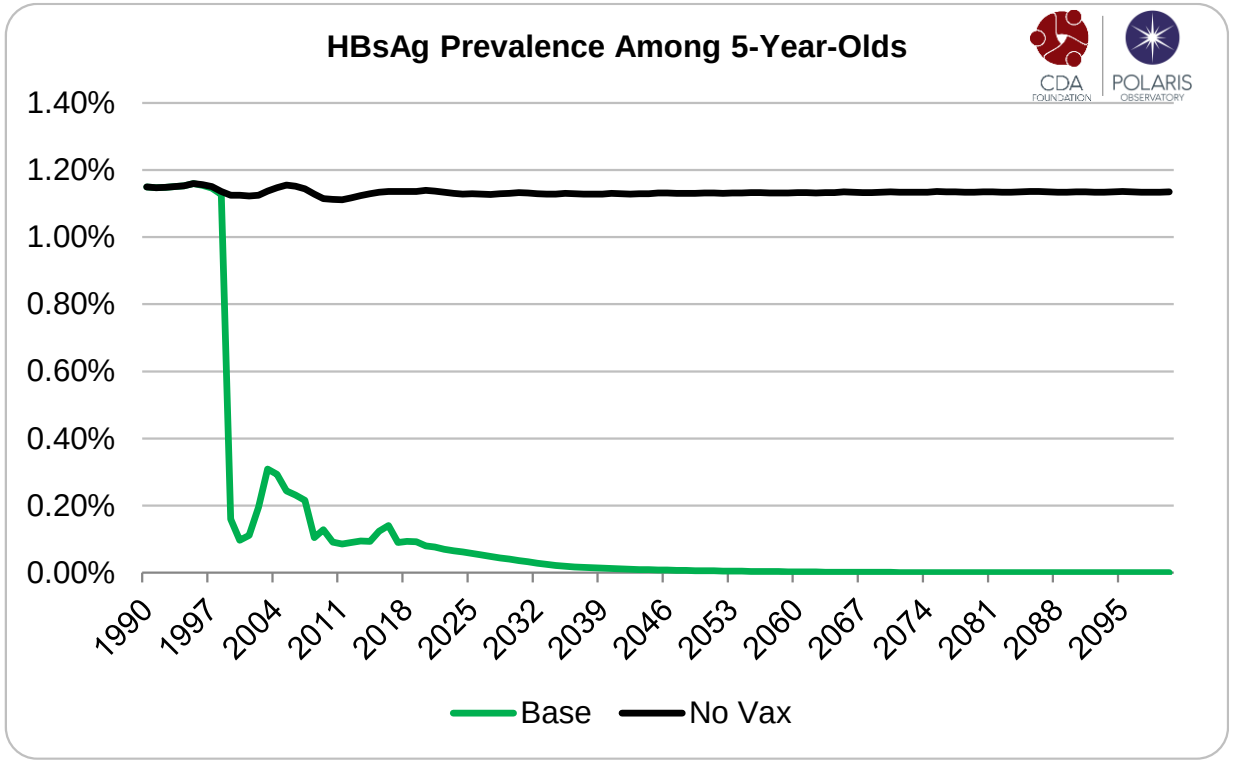
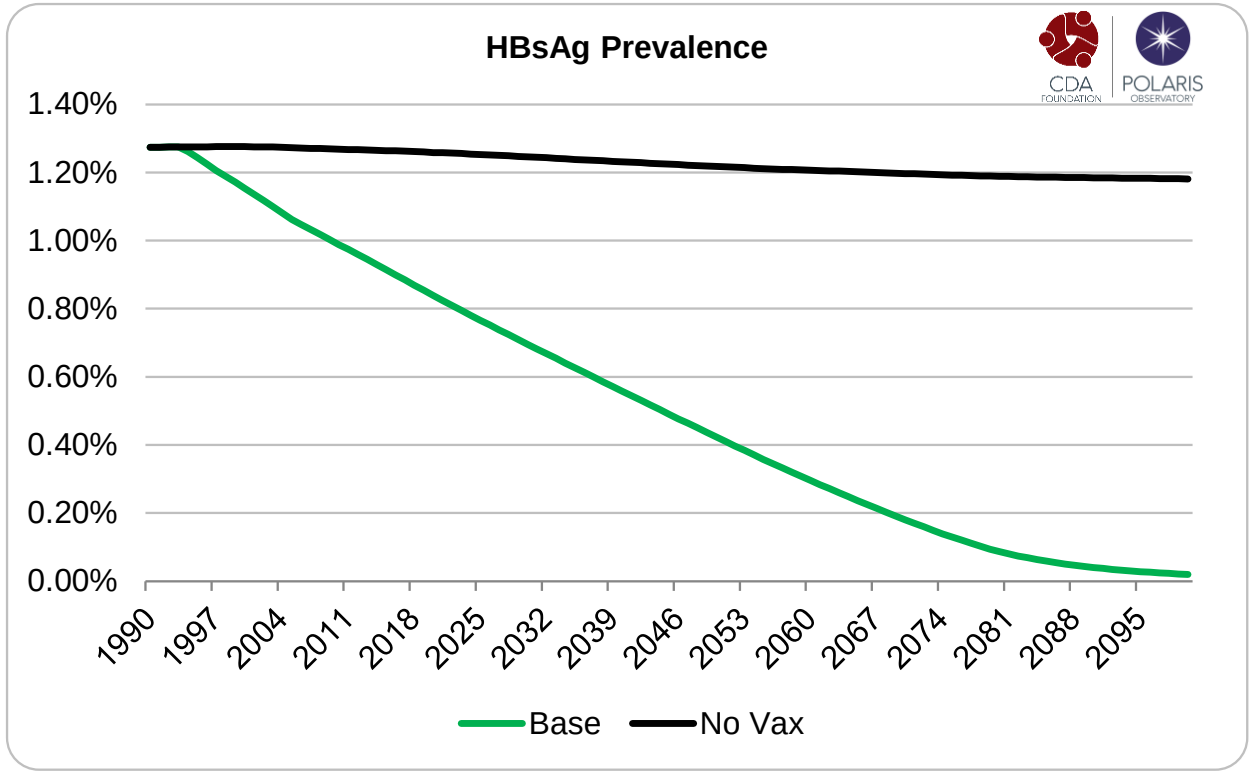
Inputs

- **Demographics:** population by age and sex 1950-2050; births&mortality rates
- **National prevalence studies**
- **Programmatic and epidemiologic data**: vaccination coverage, results of blood screening in blood banks, HBsAg screening among pregnant women, institutional deliveries, antiviral treatment among pregnant women, gammaglobulin prophylaxis in exposed children.
- **Surveillance data:** New and cumulative cases
- **Treatment information**: coverage and medicines used
- **Cost of diagnostics and treatment.**

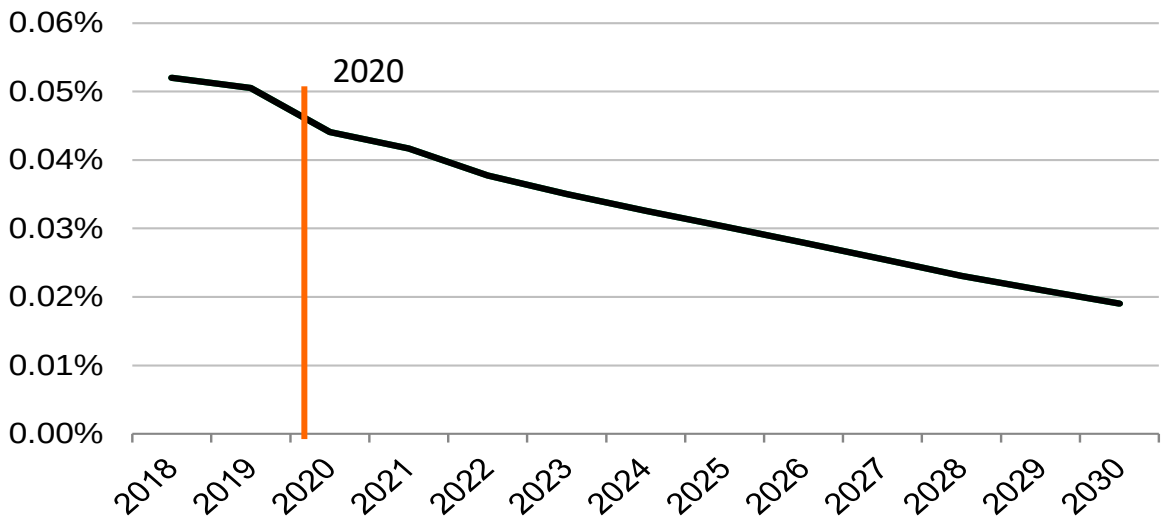
When historical and current prophylaxes efforts are considered, the impact on prevalence is seen almost immediately





Mathematical model projects 5-year-old HBsAg prevalence in Colombia achieving the impact target 2020 (≤0.1%)

HBsAg prevalence among 5-year-old of 0.05% in 2019



Serosurvey and mathematical model are in agreement

Conclusions

Information for Colombia

- High quality survey conducted in areas assessed at high risk found no infected children → highly likely that prevalence is at/below elimination target.
- High levels of immunization coverage in these areas further supports this conclusion.
  - ✓Some gaps and disparities in immunization coverage remain.
- Results are for surveyed areas only → but rationale that if high risk areas, many of which are remote and/or economically challenged, meet target, rest of country also likely to have met target.
- Mathematical modelling indicate high levels of immunization coverage resulted in almost immediate decline in hepatitis B prevalence in children and suggest current prevalence is below elimination target.

Conclusions

Lessons learned re: 2 phased approach

Risk assessment dependent upon quality and/or completeness of available data

- Prevalence data not available for all areas and differences in methods/populations/time periods limits comparability
- Some important indicators (timely hepB BD and maternal screening rates) not available -- > systems for collecting necessary information would facilitate these types of evaluations

Survey design challenges

- Focused survey increases likelihood of identifying pockets of remaining transmission → but no information about rest of the country
- Sample size sufficient to reliably 'fail' survey areas if underlying prevalence was 0.4% or higher… but small likelihood of 'passing' areas where underlying prevalence is greater than 0.1% but less than 0.4%.
    - Compromise based on available resources vs. programmatic requirements.
- Many areas likely to be at highest risk are hard to reach/not well mapped → Considerable resources required to survey these areas

Not a 'one size fits all' solution –

- May work in some settings but not all.
- Requires tailoring to setting in which it is applied

Conclusions

Lessons learned re: Investment Case

Data requirements

- Model requires substantial amount of data from many different sources
- Outputs dependent upon quality and/or completeness of available data
- Long time series are the most useful datasets, but not always available.
- Representative population-based studies at two time points still needed to validate the model. However, models can inform decisions in between.

Consensus process

- Participation of experts with knowledge of clinical and public health aspects of hepatitis in the community is essential for assessment and interpretation of input data, development of scenarios and validation of results

Scenario development

- Requires participation of decision makers to get useful results and options for implementation.
- Needs knowledge on current spending, available resources and normative to make it feasible

Conclusions

Final thoughts

- Combination of two approaches provided substantial insights to current national HBV prevalence, epidemiological and economic projections.
- Could confirm EMTCT of HBV in Colombia and quantify the return on investment of this public health achievement.
- Substantial effort and resources required to carry out both activities
- Things to consider:
  - Plan for verification
    - Consider what information sources already available that may be useful
    - Establishment of systems for routine collection of necessary input data would facilitate use of either/both/other approach
  - ‘Triangulation’ using different data/methods may provide strongest conclusion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Thank you!
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- Survey teams

DANE

Participating communities, families and children

Phase 2: Serosurvey

Powered for 'classification'*

- Smaller sample sizes than when aim to provide a precise estimate of prevalence.
- Useful when objective to classify coverage as being above or below a certain level.

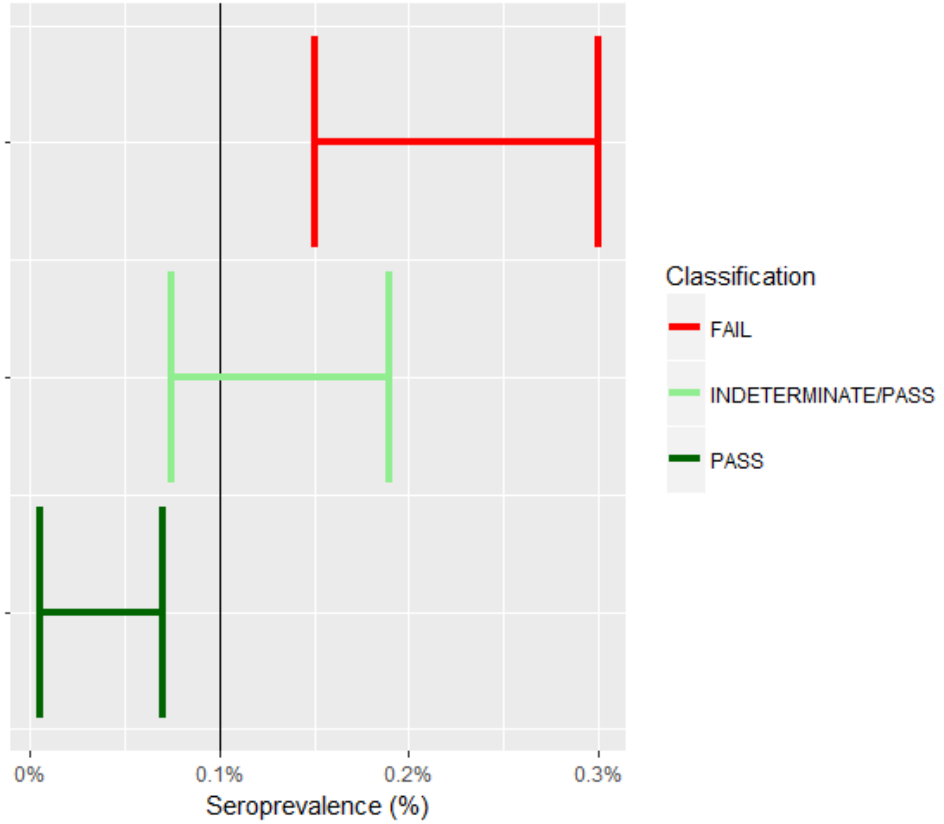
Null hypothesis

- HO: HBsAg prevalence is ≤ 0.001
- HA: HBsAg prevalence is > 0.001 (alternative prevalence = 0.004)

Analysis and interpretation

- Two 1-sided confidence bounds (95% upper confidence bound [UCB] and 95% lower confidence bound [LCB])
  - **FAIL** if the LCB > 0.1% → prevalence in areas likely above 0.1%
  - **PASS** if the LCB ≤ 0.1% → areas classified as having reach PAHO elimination target
    - The PASS can be divided into 2 sub-categories:
    - If **UCB is < 0.1%** → prevalence is likely < 0.1%.
    - If **0.1% falls between the LCB and UCB** → cannot conclude definitely that the prevalence is < 0.1%, but that it is likely < 0.4%.

Calculate a (1-2*alpha)% confidence interval accounting for survey design



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2019 Estimated prevalence

Estimated Prevalence:
0,73%

Estimated cases:
347.580