Modeling Optimal Laboratory Testing Strategies for Bacterial Meningitis Surveillance in Africa

Joseph Walker,1,2* Heidi M. Soeters,2,9 Ryan Novak,2 Alpha Oumar Diallo,2,4 Jeni Vuong,2,4 Brice Wilfried Bicaba,3 Isaie Medah,3 Issaka Yaméogo,3 Rasmata Ouédraogo- Traoré,4 Kadija Gamougone,2 Daoula Doumagoum Moto,2 Asséto Y. Dembéélé,7 Ibrehima Gindo,7 Souleymane Coulibaly,7 Djibo Issifou,2 Maman Zanelidou,2 Hamadi Assane,2 Christelle Nikiema,9 Adodo Sadji,9 Katya Fernandez,9 Jason M. Mwenda,10 Andre Bita,10 Clément Lingani,2 Haoua Tall,2 Félix Tarbandgo,3 Guetwende SAWADOGO,3 Marietou F. PAYE,17 Xin Wang,2 and Lucy A. McNamara2,9

DOI: 10.1093/infdis/jiab154

Since 2010, the introduction of an effective serogroup A meningococcal conjugate vaccine has led to the near-elimination of invasive Neisseria meningitidis serogroup A disease in Africa’s meningitis belt. However, a significant burden of disease and epidemics due to other bacterial meningitis pathogens remain in the region. High-quality surveillance data with laboratory confirmation is important to monitor circulating bacterial meningitis pathogens and design appropriate interventions, but complete testing of all reported cases is often infeasible. Here, we use case-based surveillance data from 5 countries in the meningitis belt to determine how accurately estimates of the distribution of causative pathogens would represent the true distribution under different laboratory testing strategies. Detailed case-based surveillance data was collected by the MenAfriNet surveillance consortium in up to 3 seasons from participating districts in 5 countries. For each unique country-season pair, we simulated the accuracy of laboratory surveillance by repeatedly drawing subsets of tested cases and calculating the margin of error of the estimated proportion of cases caused by each pathogen (the greatest pathogen-specific absolute error in proportions between the subset and the full set of cases). Across the 12 country-season pairs analyzed, the 95% credible intervals around estimates of the proportion of cases caused by each pathogen had median widths of ±0.13, ±0.07, and ±0.05, respectively, when random samples of 25%, 50%, and 75% of cases were selected for testing. The level of geographic stratification in the sampling process did not meaningfully affect accuracy estimates. These findings can inform testing thresholds for laboratory surveillance programs in the meningitis belt.

Keywords. Bacterial Meningitis; Laboratory Surveillance; Modeling; Burkina Faso; Chad; Mali; Niger; Togo.

Bacterial meningitis is a deadly disease with case fatality ratios that can reach 70% without rapid treatment; up to 20% of survivors experience persistent physical or cognitive disability [1]. Globally, the most common causes of bacterial meningitis are Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae [2, 3], with the highest incidence of disease observed in Africa’s “meningitis belt,” the semi-arid region south of the Saharan Desert [4]. Meningitis dynamics are highly seasonal within the belt with the period of highest risk coinciding with the dry season, generally extending from December to June. In addition to seasonal outbreaks of disease, the belt also intermittently experiences larger epidemics driven by the circulation of highly invasive pathogen strains [5]. Historically, most epidemics of meningitis in the belt were caused by N. meningitidis serogroup A (NmA) [6]. Between 2010 and 2018, meningococcal A conjugate vaccine (MACV) was introduced in 22 of the 26 countries in the meningitis belt through mass vaccination campaigns immunizing close to 300 million people aged 1–29 years of age. As of the end of 2018, 8 of the countries that conducted a mass campaign have also introduced MACV as a routine childhood vaccination through the Expanded Program on Immunization [7]. As a result of the widespread rollout of MACV, serogroup A meningococcal disease has been nearly eliminated from the meningitis belt [8–10]. However, other pathogens have emerged as the primary

*Correspondence: Lucy A. McNamara, Meningitis and Vaccine Preventable Diseases Branch, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30329 (lxf4@cdc.gov).

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1093/infdis/jiab154

The Journal of Infectious Diseases 2021;224(3):S218–27

S218 • JID 2021;224 (Suppl 3) • Walker et al
causes of bacterial meningitis outbreaks and disease in the belt, including N. meningitidis serogroups C, W, and X and S. pneumoniae.

The MenAfriNet Consortium has partnered with the Ministries of Health of Burkina Faso, Chad, Mali, Niger, and Togo since 2014 to implement meningitis case-based surveillance [11]. Efficient laboratory confirmation is a critical component of meningitis case-based surveillance to monitor epidemiologic trends of circulating bacterial meningitis pathogens, evaluate existing vaccines and other public health interventions, and inform policy decisions and development of new vaccines. However, specimen collection, transport, and testing all require public health and laboratory resources that are in limited supply in many parts of the meningitis belt. Thus determining the minimum level of specimen collection and laboratory testing necessary for public health action could help to conserve and allocate limited resources. In this analysis, we use case-based surveillance data from the 5 MenAfriNet countries to model the expected accuracy of pathogen-specific meningitis burden estimates at different levels of laboratory testing.

METHODS

Surveillance System

This analysis used 2014–2017 MenAfriNet meningitis case-based surveillance data [11]. Participating ministries of health collect case-level demographic, clinical, and laboratory data from cerebrospinal fluid (CSF) specimens for meningitis cases in selected districts. By 2017, case-based meningitis surveillance through MenAfriNet covered approximately 32.7 million people living in all districts in Burkina Faso and 115 (33%) of 347 districts in Chad, Mali, Niger, and Togo [12]. Bacterial meningitis cases are classified using case definitions established by the World Health Organization [13]. Under these criteria, suspected cases are distinguished by a sudden onset of fever above 38.5°C with ≥1 meningeal sign, such as neck stiffness, convulsions, or bulging fontanelle. For a case to be classified as confirmed, the criteria for a suspected case must be met and N. meningitidis, S. pneumoniae, H. influenzae, or another bacterial meningitis pathogen must be identified in CSF by culture or real-time polymerase chain reaction (PCR).

CSF specimens were collected from each case and transported to a national reference laboratory (NRL), either directly or first through the district and/or regional public health laboratory, either in transisolate medium at room temperature for culture and/or in a cryotube via cold chain for real-time PCR. At the NRL, culture, latex agglutination, and/or PCR testing were used to attempt to identify one of the following meningitis-associated bacterial pathogens: (1) N. meningitidis, serogroups A, B, C, W, X, or Y; (2) S. pneumoniae; (3) H. influenzae, serotype b and non-serotype b; and (4) group B Streptococcus. PCR targeted the sodC gene for N. meningitidis, lytA for S. pneumoniae, and hpd for H. influenzae. Confirmed cases of group B Streptococcus were identified via culture.

A total of 2673 cases were tested with both culture and PCR. Of these, 957 (35.8%) were positive by one or both methods: 936 (35.0%) by PCR, 306 (11.4%) by culture, and 285 (10.7%) by both. In the 60 cases (2.2%) in which PCR and culture testing identified different pathogens, the PCR result was used because of its higher sensitivity, low contamination rate among PCR specimens in the MenAfriNet network [12], and implementation of external quality control to ensure reliability of PCR results. If culture was not performed at the NRL, the culture result reported from the district or regional laboratory was used, if available (167 of 3077 cases [5.4%] with a culture result). N. meningitidis–positive specimens for which serogroup could not be determined were classified as serogroup-indeterminate, a category which includes both non-ABCWXY serogroups and nongroupable (unencapsulated) strains of N. meningitidis.

Statistical Analysis

Each case was assigned a date based on the day of consultation at the health center. If this field was missing, the date of CSF collection was used in its place. For cases missing both of these fields (n = 6), the date the specimen arrived at the NRL was used. We then grouped cases into distinct country-seasons, which we defined as the period from 1 November of one year to 31 August of the subsequent year in a specific country. We selected this period, which includes 97% and 99% of suspected and confirmed cases, respectively, on the basis that it would capture the typical meningitis season (approximately December–June) and seasons with unusually early or late timing [4, 14, 15]. Cases were included only if they were reported from a district participating in MenAfriNet, and country-seasons containing <30 confirmed cases were excluded from the analysis (Figure 1). Suspected meningitis cases with specimens that underwent culture and/or PCR testing at a NRL were classified as either confirmed or unconfirmed based on the above case definition. For each confirmed case, we defined the causative pathogen as the pathogen species and serogroup/serotype (where applicable) identified by PCR (n = 3959), or by culture if PCR results were unavailable or negative (n = 59). For this analysis, H. influenzae serotype b and non-serotype b were treated as distinct pathogens, as were individual N. meningitidis serogroups (A, B, C, W, X, Y, and indeterminate). S. pneumoniae and group B Streptococcus were each treated as a single pathogen in this analysis, as the serotypes of these pathogens were not routinely reported.

Using data on laboratory-tested cases, we sought to determine how accurately estimates of the distribution of causative pathogens would represent the true distribution under different laboratory testing strategies. To simulate the distributions of causative pathogens that may be observed with less-complete testing, we selected subsets of cases with CSF specimens tested...
via PCR or culture (tested cases) from each country-season using both a random- and a sequential-sampling testing strategy. Under the random-sampling testing strategy, we constructed 3 geographic sampling levels or strata by generating subsets of tested cases at the country, region, and district level. We formed the country sampling level by randomly selecting \( p \% \) of tested cases (testing coverage level) from a country-season. Similarly, we generated the region-stratified and district-stratified sampling levels by randomly selecting \( p \% \) of tested cases from each region and each district of the country in a given season, respectively. If \( p \% \) of tested cases was not an integer value, we rounded down to the nearest whole case. For each country-season, geographic-sampling level (unstratified, region-stratified, and district-stratified), and testing coverage level, ranging from \( p = 5\% \) to \( p = 100\% \) (5\% increments), we selected 2000 random subsets of cases to allow error estimation (see below).

For a given country-season, the random-sampling strategy would be expected to provide an unbiased estimate of the true pathogen distribution among confirmed cases. In practice, however, timely outbreak identification and response requires that laboratory results be obtained and reported regularly over the course of the season [13], precluding selection of a truly random sample of specimens for testing. To assess the potential impact of nonrandom selection of cases for testing, we implemented 3 forms of sequential sampling (unstratified, region-stratified, and district stratified) as complements to the random sampling analysis. Under sequential sampling, we selected the first \( p \% \) of tested cases observed within each geographic stratum (the entire country-season, each region, and each district), with values of \( p \) on the interval from \( p = 5\% \) to \( p = 100\% \) (2.5\% increments). Because the sequential sampling method was nonrandom, only a single subset was generated for each combination of country-season, geographic stratum, and testing coverage level.

For each country-season and sampling strategy, we first calculated the proportion of confirmed cases associated with each pathogen for each subset of tested cases (“estimated pathogen proportions”) as well as in the full set of tested cases (“true pathogen proportions”). Then we calculated the margin of error of pathogen proportion estimates (“margin of error”) for each subset, which we define as the greatest absolute error of the pathogen proportion estimates (relative to the true pathogen proportion) from a given subset. Thus, all pathogen proportion estimates from a subset are within the subset's margin of error of the true values.

For each unique random sampling strategy, defined by the proportion of cases selected for testing and the level of geographic stratification, we defined 2 distinct margin of error summary values: (1) the average margin of error, calculated by averaging the absolute value of the margin of error across each of the 2000 subsets; and (2) the 95\% credible margin of error, calculated by taking the 95th percentile margin of error value across all 2000 random subsets. The latter provides an estimate of the level of accuracy that one could expect to achieve with 95\% confidence for the random-sampling strategy.

For each sequential subset, we derived a single margin of error value, the sequential margin of error, defined as the greatest absolute difference in pathogen proportion values between the subset and the full set of cases. For each summary value, the median across the 12 included country-seasons was presented.

Documenting the presence or absence of rare pathogen strains in a population requires the collection of a sufficient number of representative samples—more than are needed to
document comparatively common strains—efficient specimen transport, and quality laboratory testing. Pathogens of interest may include emerging strains as well as those that have been locally controlled or eliminated through vaccination, such as NmA after the mass rollout of MACV in meningitis belt countries. Using NmA in the Burkina Faso 2014–2015 season as a case study [16], we estimated the probability of detecting ≥1 of the 4 NmA cases that occurred in that country-season (the proportion of random subsets containing ≥1 NmA cases) for different levels of testing coverage and geographic stratification.

In addition to pathogen-specific measures, the overall proportion of tested cases that are confirmed as bacterial meningitis (test-positive proportion) is an important metric of meningitis activity and surveillance system functioning. To assess the accuracy of the test-positive proportion under different sampling strategies, we also calculated the absolute margin of error of the test-positive proportion in each subset at different levels of testing coverage and geographic stratification for each country-season.

Data were analyzed using R version 3.5.1. Analysis of data collected through routine MenAfriNet surveillance was determined by the Human Research Protection Office of the Centers for Disease Control and Prevention to be public health nonresearch, and institutional review board review was not required by any participating institutions.

RESULTS
Descriptive Epidemiology
Case-based surveillance data were available for 12 MenAfriNet country-seasons: the 2016–2017 season in Chad, the 2014–2015, 2015–2016, and 2016–2017 seasons in Burkina Faso, Niger, and Togo, and the 2015–2016 and 2016–2017 seasons in Mali. In total, 17 237 suspected cases of meningitis were reported in MenAfriNet districts during these seasons [Table 1]. Data from the 2014–2015 and 2015–2016 seasons were not available for Chad, which joined the MenAfriNet consortium in 2016. We did not include the 2014–2015 Mali season in this analysis because only 2 confirmed cases were reported during this season in MenAfriNet districts.

PCR or culture was performed at an NRL on specimens from 68% (11 721 of 17 237) of suspected cases overall, with proportions of cases tested ranging from 55.8% in Niger during the 2014–2015 season to 96.7% in Chad during the 2016–2017 season. Across all countries and seasons, a causative pathogen was confirmed in 34.3% of tested case specimens (4018 of 11 721), with the confirmation percentage ranging from 20.6% in Niger during the 2015–2016 season to 53.8% in Togo during the 2016–2017 season. The greatest number of seasonal reported cases in our data set occurred in Niger during the 2014–2015 meningitis season (3503 suspected and 664 confirmed cases among MenAfriNet districts), which experienced an epidemic of N. meningitidis serogroup C ST-10217 [17].

In all country-seasons, N. meningitidis or S. pneumoniae was the most common bacterial species identified in specimens from confirmed cases [Table 1]. Cases attributable to H. influenzae were comparatively uncommon, comprising only 4.1% (n = 165) of all confirmed cases; 65.0% of these were H. influenzae type b (n = 107). The most common serogroup among the 2266 confirmed N. meningitidis cases was C (54.2%, n = 1229) followed by W (29.9%, n = 678) and X (13.7%,

| Table 1. Bacterial Meningitis Cases by Season and Country in MenAfriNet Data Set |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Countries by Season | Suspected Cases, No. | Tested Cases |Confirmed Cases |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Burkina Faso |
| 2014–2015 | 2454 | 1795 (73.1) | 741 (41.3) | 262 (35.4) | 453 (61.1) | 26 (3.5) |
| 2015–2016 | 2427 | 1805 (74.4) | 683 (37.8) | 161 (23.6) | 484 (70.9) | 38 (5.6) |
| 2016–2017 | 2512 | 1751 (69.7) | 559 (31.9) | 174 (31.1) | 353 (63.1) | 32 (5.7) |
| Chad |
| 2016–2017 | 120 | 116 (96.7) | 54 (46.6) | 22 (40.7) | 26 (48.1) | 6 (11.1) |
| Mali |
| 2015–2016 | 290 | 262 (90.3) | 71 (27.1) | 26 (37.1) | 35 (50.0) | 9 (12.9) |
| 2016–2017 | 240 | 214 (73.8) | 47 (22.0) | 6 (12.8) | 22 (46.8) | 19 (40.4) |
| Niger |
| 2014–2015 | 3503 | 1954 (55.8) | 663 (33.9) | 583 (879) | 72 (10.9) | 8 (1.2) |
| 2015–2016 | 1798 | 1301 (72.4) | 268 (20.6) | 226 (84.3) | 33 (12.3) | 9 (3.4) |
| 2016–2017 | 3088 | 1933 (62.6) | 686 (35.5) | 607 (88.5) | 63 (9.2) | 16 (2.3) |
| Togo |
| 2014–2015 | 73 | 68 (93.2) | 32 (47.1) | 20 (62.5) | 12 (37.5) | 0 (0) |
| 2015–2016 | 291 | 273 (93.8) | 80 (29.3) | 67 (83.8) | 12 (15.0) | 1 (1.3) |
| 2016–2017 | 441 | 249 (56.5) | 134 (53.8) | 112 (83.6) | 21 (15.7) | 1 (0.8) |
| Total (all countries and seasons) | 17 237 | 11 721 (68.0) | 4018 (34.3) | 2266 (56.4) | 1586 (39.48) | 165 (4.1) |
n = 311) (Figure 2). Serogroups A and Y were detected in only 4
and 3 cases, respectively, and no cases of confirmed serogroup B
disease were observed. Serogroup could not be determined for
1.8% (n = 41) of confirmed meningococcal meningitis cases.
Only 1 confirmed case of group B Streptococcus meningitis was
reported, in the 2015–2016 Mali season.

Estimating the Relative Burden of Causative Pathogens

To understand the trade-off between accurately
understanding bacterial meningitis epidemiology and conserving
resources by limiting laboratory testing, we compared patho-
gen proportion estimates generated from subsets of tested
cases to the true proportions generated from the full set of
tested cases in each country-season. Figure 3 shows distri-
butions of the margin of error of pathogen proportion esti-
mates at various levels of testing. When random, unstratified
sampling is performed in the median (interquartile range
[IQR]) country-season, pathogen proportion estimates have
an average margin of error (the greatest absolute error across
pathogens) of 0.06 (0.03–0.12), 0.04 (0.02–0.07), and 0.02
(0.01–0.04) when 25%, 50%, and 75% of cases are tested,
respectively. That is, when half of cases are randomly selected
for testing in the median country-season analyzed, the most erroneous pathogen propor-
tion estimate has an absolute error ≤0.07 in 95% of random sam-
plies. These median 95% credible margin of error values are over
twice as high as the associated medians of the average margin of
error. Random sampling with geographic stratification, either
by region or health district, did not produce meaningfully dif-
ferent values of the average, sequential, or 95% credible margins
of error.

Regardless of the sampling method or level of geographic
stratification, we observed that the country-seasons with the
least precise estimates of relative pathogen burden were those
in which there were relatively few cases with an available labora-
tory testing result (Supplementary Figure 1 and Supplementary
Table 1). In the 6 analyzed country-seasons in which between
68 and 273 cases were tested, the median margin of error values
were consistently over twice as high as those from the 6 analyzed
country-seasons in which between 1301 and 1954 cases had a
laboratory test result. This observation was expected (refer to
Supplementary Appendix 1 for more details) and demonstrates

Figure 2. Confirmed bacterial meningitis cases by pathogen. Bar heights represent numbers of confirmed meningitis cases associated with each bacterial pathogen, pooled
across all 12 analyzed country-seasons. Abbreviations: Hi non-b, Haemophilus influenzae non–type b; Hib, Haemophilus influenzae type b; NmA, NmC, NmW, NmX, and
NmY, Neisseria meningitidis serogroups A, C, W, X, and Y, respectively; NmInd, indeterminate/unknown serogroup of N. meningitidis; Spn, Streptococcus pneumoniae.
that testing of a higher proportion of case specimens is needed to accurately understand bacterial meningitis epidemiology in the context of a lower burden of disease.

Estimating the Proportion of Tested Cases Confirmed as Bacterial Meningitis

The proportion of tested cases that were confirmed as bacterial meningitis (the “test-positive proportion”) is an important surveillance indicator used to understand bacterial meningitis disease burden as well as surveillance system functioning for a given location and period of time [12]. This proportion has a fixed value for a given location and time period when all suspect cases are tested, but is subject to variability when random subsets of cases are selected for testing (Figure 4). When random, unstratified sampling is performed in the median country-season analyzed, the estimated test-positive proportion differs
from the true value by 0.02 in the average sample, and differs by ≤0.04 in 95% of samples.

Sequentially selecting cases over the observation period produced the least accurate test-positive proportion estimates: in the median country-season analyzed, the observed absolute error of the test-positive proportion is 0.05 (IQR, 0.01–0.09), 0.06 (0.03–0.08), and 0.04 (0.03–0.05) when the first 25%, 50%, and 75% of cases are sequentially selected for testing without geographic stratification. Stratifying the sampling process by region or district did not produce meaningfully different results.

**Case Study: Detecting Rare NmA Cases in the Burkina Faso 2014–2015 Season**

During the 2014–2015 meningitis season in Burkina Faso, a total of 2454 suspected cases were reported. Laboratory testing was performed on specimens from 1795 (73.1%) of these cases, resulting in the confirmation of 4 NmA cases. Given the importance of detecting rare NmA cases via surveillance, as they provide evidence of NmA transmission, we evaluated the probability of detecting ≥1 of these NmA cases under different random testing strategies. With random unstratified samples of 25%, 50%, and 75% of tested cases, the probabilities of detecting
≥1 of the NmA cases were 0.71, 0.93, and 0.99, respectively. Gains in the sensitivity of random testing beyond 50% sampling were minimal, and the level of geographic stratification in the sampling process did not meaningfully affect our findings [Figure 5].

DISCUSSION

This analysis explored the accuracy of pathogen proportion estimates from meningitis case-based surveillance at different levels of testing coverage and geographic stratification in countries of the African meningitis belt. Our findings suggest that in approximately three-quarters of country-seasons, testing a random sample of 50% of suspected meningitis cases would be sufficient to estimate the true percentage of cases caused by each pathogen within 7% on average, and within 13% with 95% confidence. At 50% testing coverage or higher, sampling cases sequentially from the start of the season instead of randomly did not meaningfully affect the accuracy of pathogen proportion estimates in the country-seasons analyzed. This suggests that even with nonrandom sampling, testing of specimens from ≥50% of cases would still provide reliable insight into different pathogens’ relative contributions to the burden of bacterial meningitis. The estimates of the proportion of cases caused by each pathogen were found to be more accurate during seasons with a large number of tested cases (>1300) than in seasons with relatively few (68–273) tested cases. This is consistent with our expectation that the variance of a pathogen proportion estimate is inversely related to the total number of tested cases in a country-season.

In addition to estimating the overall burden of different pathogens based on subsets drawn from each country-season, we used data from the Burkina Faso 2014–2015 season to estimate the probability of detecting ≥1 case of a rare and important pathogen at different testing levels. In this season, in which NmA was detected in 4 of 1805 tested cases, we estimated that ≥1 NmA case would have been detected 93% of the time with random sampling of 50% of suspected cases. We also found that when 50% of suspected cases are randomly selected for testing, estimates of the true prevalence of laboratory-confirmable bacterial meningitis among tested cases have a low mean absolute error of <2.5% in about 75% of country-seasons. This analysis suggests that testing approximately half of case specimens would yield both relatively accurate estimates of the distribution of causative pathogens, as well as high sensitivity to detect rare but important pathogens such as NmA.

A number of factors could cause the performance of laboratory surveillance in practice to systematically differ from the estimates we provide here. In each country-season analyzed, our sampling frame consisted of the set of tested cases in the districts covered by MenAfriNet case-based surveillance. For Burkina Faso, all districts nationwide conduct case-based surveillance; however, in the remaining countries only a subset of districts implemented meningitis case-based surveillance in the years covered in our data. Given the inverse relationship we describe between the total number of cases tested and the error of pathogen-specific burden estimates, accuracy targets could be achieved by testing a lower proportion of cases than estimated in our analysis if the sampling frame was expanded to include suspected cases in additional districts. Conversely, if the introduction of next-generation meningococcal conjugate vaccines significantly reduces the overall number of suspected bacterial meningitis cases, testing a lower proportion of cases could still yield reliable estimates of the burden of different pathogens.
estimates of relative pathogen burden may become biased, particularly when testing coverage is low, if surveillance programs do not take steps to eliminate systematic differences between tested and untested cases. Systematic sampling methods, such as testing every nth suspected case at each facility, can be efficient yet minimally biased alternatives to true random sampling, and are frequently used in laboratory surveillance systems for influenza [19]. Ensuring uniform surveillance across the districts of a country can also help reduce bias in the estimates of circulating pathogens. Surveillance programs may wish to create indicators to monitor the consistency of testing coverage over space and time within the season, and adjust their sampling strategy as necessary.

Strategies of preferentially testing specimens that are more likely to be confirmed—e.g., CSF specimens that are cloudy or purulent, or that are collected from more severe cases—could increase the sensitivity for detecting rare pathogens and the precision of pathogen proportion estimates. However, this form of selection could also bias pathogen proportion estimates if the features used to prioritize specimens for testing are more common in cases caused by some pathogens than others. The test-positive proportion would also be inflated under preferential testing, and would no longer represent the positive predictive value of the suspected case definition for bacterial meningitis.

In addition to the above limitations, MenAfriNet case-based surveillance was initiated in 2014, which meant that data were only available for 12 country-seasons. This limited our ability to evaluate how surveillance performance is affected by additional factors such as the number of dominant circulating pathogens, spatial differences in pathogen burden between regions and districts, and temporal changes in epidemiology over the course of the season.

For this analysis, our objective was to assess the ability of case-based meningitis surveillance to accurately estimate the true distribution of causative meningitis pathogens, as retrospectively assessed at the end of a given meningitis season, when a reduced proportion of patient specimens are collected and tested. We did not consider the testing coverage needed to adequately perform other objectives of laboratory surveillance, such as early detection of outbreaks and epidemics and rapid determination of the causative pathogen(s), identification of differences in pathogen burden between geographic areas or periods of time within a season, or monitoring more detailed data such as antibiotic resistance or the spread of specific strains. By quantifying how discrepant subset-based estimates are from “true” values based on the full set of tested cases, future analyses could adapt our modeling framework to estimate the performance of laboratory surveillance for additional objectives.

Case-based meningitis surveillance is highly valuable to develop a comprehensive understanding of bacterial meningitis epidemiology that can be used to evaluate current public health interventions and inform policy and vaccine development. However, it is also expensive and challenging in resource-limited settings. If an accurate understanding of meningitis etiology can be gained with a lower specimen collection and testing target, this could reduce the overall burden and resources required for specimen collection, transport, and testing and improve the efficiency of the surveillance system. Our estimates of the accuracy of pathogen proportion estimates generated from subsets of cases, when considered alongside the goals of the surveillance program and resource availability, can be used to set targets for the proportion of case specimens that require confirmatory testing during routine and epidemic meningitis seasons in the meningitis belt. Preliminary findings from this analysis were used to update the 2018 World Health Organization standard operating procedures for meningitis surveillance in Africa [13]. However, our findings also demonstrate that it will be important to revisit this surveillance guidance if the introduction of new vaccines or other interventions leads to substantial reductions in the burden of bacterial meningitis in this region.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Notes**

**Acknowledgments.** The MenAfriNet Consortium is an international consortium led and implemented by Ministère de la Santé du Burkina Faso, Ministère de la Santé et de l’Hygiène Publique du Mali, Ministère de la Santé Publique du Niger, Ministère de la Santé Publique du Tchad, Ministère de la Santé et de la Protection Sociale du Togo, Agence de Médecine Préventive, the Centers for Disease Control and Prevention, and the World Health Organization, with support and collaboration from other international and nongovernmental organizations. The authors thank all MenAfriNet partners, including participating national health systems, health centers, and laboratories.
Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Supplement sponsorship. This supplement is sponsored by the World Health Organization and the U. S. Centers for Disease Control and Prevention.

Financial support. This work was supported by the MenAfriNet Consortium through a grant from the Bill & Melinda Gates Foundation (grant OPP1084298).

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med 2001; 344:1378–88.
2. Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: a systematic review and meta-analysis. PLoS One 2018; 13:e0198772.
3. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392:1789–858.
4. Greenwood B. Manson lecture: meningococcal meningitis in Africa. Trans R Soc Trop Med Hyg 1999; 93:341–53.
5. Agier L, Martiny N, Thiongane O, et al. Towards understanding the epidemiology of Neisseria meningitidis in the African meningitis belt: a multi-disciplinary overview. Int J Infect Dis 2017; 54:103–12.
6. World Health Organization. Meningococcal disease in countries of the African meningitis belt, 2012—emerging needs and future perspectives. Wkly Epidemiol Rec 2013; 88:129–36.
7. Bwaka A, Bita A, Lingani C, et al. Status of the rollout of the meningococcal serogroup A conjugate vaccine in African meningitis belt countries in 2018. J Infect Dis 2019; 220:S140–7.
8. Kristiansen PA, Diomandé F, Ba AK, et al. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. Clin Infect Dis 2012; 56:354–63.
9. Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. Lancet 2014; 383:40–7.
10. Novak RT, Kambou JL, Diomandé FVK, et al. Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data. Lancet Infect Dis 2012; 12:757–64.
11. Patel JC, Soeters HM, Diallo AO, et al. MenAfriNet: a network supporting case-based meningitis surveillance and vaccine evaluation in the meningitis belt in Africa. J Infect Dis 2019; 220:S148–54.
12. Mbaeyi SA, Lingani C, Diallo AO, et al. Improving case-based meningitis surveillance in 5 countries in the meningitis belt in sub-Saharan Africa, 2015–2017. J Infect Dis 2019; 220:S155–64.
13. World Health Organization, Regional Office for Africa. Standard operating procedures for surveillance of meningitis preparedness and response to epidemics in Africa. Brazzaville, Republic of Congo: WHO-AFRO; 2018.
14. Zunt JR, Kassebaum NJ, Blake N, et al. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018; 17:1061–82.
15. Desmond NA, Nyirenda D, Dube Q, et al. Recognising and treatment seeking for acute bacterial meningitis in adults and children in resource-poor settings: a qualitative study. PLoS One 2013; 8:e68163.
16. Diallo AO, Soeters HM, Yameogo I, et al. Bacterial meningitis epidemiology and return of Neisseria meningitidis serogroup A cases in Burkina Faso in the five years following MenAfriVac mass vaccination campaign. PLoS One 2017; 12:e0187466.
17. Sidikou F, Zaneidou M, Alkassoum I, et al. Emergence of epidemic Neisseria meningitidis serogroup C in Niger, 2015: an analysis of national surveillance data. Lancet Infect Dis 2016; 16:1288–94.
18. Alderson MR, LaForce FM, Sobanjo-ter Meulen A, Hwang A, Preziosi MP, Klugman KP. Eliminating meningococcal epidemics from the African meningitis belt: the case for advanced prevention and control using next-generation meningococcal conjugate vaccines. J Infect Dis 2019; 220:S274–8.
19. World Health Organization. Global epidemiological surveillance standards for influenza. Geneva, Switzerland: World Health Organization; 2014.