Practice of Epidemiology


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Incident cases of tuberculosis may result from a recently acquired *Mycobacterium tuberculosis* infection or from the reactivation of a latent infection acquired in the remote past. The authors used molecular fingerprinting data to estimate the relative contributions of recent and remotely acquired infection to the yearly incidence of tuberculosis in Arkansas, a state with a largely rural population where the incidence of tuberculosis declined from 7.9 cases per 100,000 population to 4.7 cases per 100,000 between 1997 and 2003. The authors used a time-restricted definition of clustering in addition to the standard definition in order to increase the specificity of the clustering measure for recent transmission. The greatest overall declines were seen in non-Hispanic Blacks (from 13.8 cases per 100,000 in 1997 to 6.5 cases per 100,000 in 2003) and persons aged 65 years or more (from 19.9 cases per 100,000 in 1997 to 8.5 cases per 100,000 in 2003). In both groups, the incidence of nonclustered cases declined more dramatically than the incidence of clustered cases. This suggests that the decline in rates resulted primarily from declining rates of disease due to reactivation of past infections. Declines in the overall incidence of tuberculosis in a population may not necessarily result from declines in active transmission.

Arkansas; cohort effect; DNA fingerprinting; epidemiology, molecular; infection control; *Mycobacterium tuberculosis*; rural health; tuberculosis

Abbreviations: MSA, Metropolitan Statistical Area; RFLP, restriction fragment length polymorphism; TB, tuberculosis.

Following a resurgence in the late 1980s, the incidence of tuberculosis (TB) in the United States has been in steady decline, decreasing by 44 percent between 1993 and 2003 (1) and reaching a historic low of 4.8 cases per 100,000 population in 2005; the lowest rate since national reporting began in 1953 (2). TB incidence rates are not consistent across populations, however, and gaps in incidence between racial/ethnic groups and between US- and foreign-born persons persist (2). In order to best focus the limited resources available on the elimination of TB in the United States, it is important to understand what factors have driven the decline and how those factors vary across subpopulations.

Because of the complex natural history of TB, incident cases in a population may be due to infections that were...
acquired recently and therefore represent evidence of active chains of transmission, or they may be due to the reactivation of latent infections acquired years or even decades earlier (3). Clinically, it is difficult to distinguish between recently acquired and reactivated disease (4), but the frequency of each type in the population has important implications for infection control.

DNA genotyping of Mycobacterium tuberculosis isolates provides a tool for drawing inferences about the transmission history of a clinical isolate. Cases that produce isolates with identical or highly similar DNA genotyping patterns, identified as clusters, reflect a common chain of transmission (5) and are considered to be caused by the same strain. Clusters occurring within a short time period are considered to reflect active transmission followed by rapid progression to clinical disease. By contrast, cases involving unique isolates are considered to result from reactivation of a latent infection acquired in the past. A number of investigators have used clustering analyses to estimate the proportion of disease resulting from recent transmission (6–9), and a few have used it to obtain insight into trends in TB incidence over time. However, these latter studies have focused on urban populations (10, 11). In rural populations, the dynamics of TB transmission probably differ considerably from those of urban settings; thus, a clustering analysis of TB trends over time in a rural setting would be particularly revealing.

In Arkansas, the reported incidence of TB declined from 7.9 cases per 100,000 population in 1997 to 4.7 cases per 100,000 in 2003 (12–18). It is uncertain whether or not this decline can be attributed to a decrease in recent transmission. Using DNA genotyping data on M. tuberculosis isolates collected in Arkansas between 1996 and 2003, we estimated the relative contributions of changes in the incidence of recently acquired disease, due to active transmission in the population, and reactivation disease, due to the reactivation of infections acquired in the past, to the overall changes in TB incidence in this population between 1997 and 2003.

MATERIALS AND METHODS

Arkansas demographic characteristics

We characterized the Arkansas population using demographic information obtained from 2000 US Census data (19). National and state TB rates were obtained from Centers for Disease Control and Prevention surveillance (12–18, 20). Census Bureau Metropolitan Statistical Areas (MSAs) defined by Arkansas’ Office of Management and Budget were used to determine urban areas; non-MSAs were considered to be rural areas. The MSAs identified included Fayetteville-Springdale-Rogers, Fort Smith, Jonesboro, Little Rock-North Little Rock, Memphis, Pine Bluff, and Texarkana. All counties within these MSAs were considered urban, while all counties outside of these MSAs were considered rural.

Study population

Arkansas reported 1,402 incident cases of TB between January 1, 1996, and December 31, 2003 (12–18, 20). Of these cases, 1,025 (73.1 percent) were confirmed by bacterial culture, and 993 (70.8 percent) were genotyped. We included all 993 cases for which the initial isolate was genotyped in our analysis. To assess the representativeness of cases with genotyped isolates, we compared selected demographic and clinical data among cases for which an isolate was genotyped and cases for which no isolate was genotyped using a chi-squared test (generated with SAS, version 9.1 (21)) (table 1). If multiple isolates were collected for any single patient, only the first isolate was included in our analysis. Standard demographic information was collected using the Centers for Disease Control and Prevention’s “Report of a Verified Case of Tuberculosis” form. Annual case rates of TB were calculated per 100,000 population using yearly population estimates from the National Center for Health Statistics. Race/ethnicity was based on self-report. This study was approved by the health sciences institutional review boards of the University of Michigan and the University of Arkansas for Medical Sciences.

Genotyping

IS6110 restriction fragment length polymorphism (RFLP) patterns were determined using standard procedures, as previously described (22). For all 264 isolates with fewer than six IS6110 bands (26.5 percent of those typed) and for isolates with six or more IS6110 bands that differed from another IS6110 pattern by only one band, spoligotype patterns were also generated, following a standard protocol (23).

Cluster definition

Clusters of cases sharing identical or highly similar fingerprints may include cases for which epidemiologic evidence of recent transmission between other cases in the cluster cannot be found (24, 25) or among which epidemiologic evidence suggests a transmission event that occurred in the remote past (25). In order to increase the specificity of our clustering measure for recent transmission, we used a time-restricted definition of clustering in addition to the standard definition, which we refer to here as the “conventional” clustering definition.

A “conventional” cluster was defined as a cluster of two or more cases with isolates identified as related by IS6110 RFLP and spoligotyping. Related isolates were defined as isolates with more than five IS6110 bands with identical IS6110 RFLP patterns or IS6110 RFLP patterns differing by one band but having identical spoligotype patterns, or isolates with five or fewer bands with both identical IS6110 RFLP patterns and identical spoligotype patterns.

A case was considered part of a “time-restricted” cluster if the case isolate was clustered by the conventional definition with the isolate of another case diagnosed within the 1-year period prior to its diagnosis date. In the literature, the cutoff point used to distinguish recent disease from reactivation disease is arbitrary, ranging from 1 year (10) to as many as 5 years in some studies (26, 27). We chose a 1-year period for our definition of clustering, to obtain the greatest possible specificity and to allow our analysis to be comparable to previous reports regarding clustering trends over time (10). To assess the specificity of our time-restricted
TABLE 1. Distribution of selected demographic and clinical characteristics among reported tuberculosis cases for which a bacterial isolate was genotyped (typed) and cases for which no isolates were genotyped (nontyped), Arkansas, 1996–2003

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Typed (n = 993)</th>
<th>Nontyped (n = 409)*</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>536 54.0</td>
<td>154 37.8</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>356 35.9</td>
<td>127 31.2</td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>4 0.4</td>
<td>2 0.5</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>51 5.1</td>
<td>52 12.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>46 4.6</td>
<td>72 17.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>16 1.6</td>
<td>112 27.4</td>
<td></td>
</tr>
<tr>
<td>20–64</td>
<td>510 51.4</td>
<td>193 47.2</td>
<td></td>
</tr>
<tr>
<td>65–84</td>
<td>335 33.7</td>
<td>80 19.5</td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>132 13.3</td>
<td>24 5.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>641 64.6</td>
<td>245 59.9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>352 35.5</td>
<td>164 40.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-born</td>
<td>86 8.7</td>
<td>99 24.2</td>
<td></td>
</tr>
<tr>
<td>US-born</td>
<td>907 91.3</td>
<td>310 75.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urbanity of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>581 58.5</td>
<td>189 46.2</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>412 41.5</td>
<td>220 53.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Type of tuberculosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>854 86.0</td>
<td>317 77.5</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>139 14.0</td>
<td>92 22.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Race/ethnicity was unknown for two cases.  † Two-sided p value from a chi-squared test comparing the distributions of the characteristic between typed and nontyped isolates.

cluster definition as a measure of active transmission, we used the chi-squared test (in SAS, version 9.1 (21)) to compare the frequency distributions of commonly identified risk factors for active transmission among isolates clustered within 1 year and isolates that were clustered by the conventional definition but did not meet our 1-year time restriction (table 2).

The time-restricted cluster definition was used as our cluster definition for all of our analyses of trends over time. We refer to isolates that did not meet the time-restricted definition as "nonclustered": This includes isolates that exhibited a unique pattern by both IS6110 and spoligotyping, as well as isolates that were clustered by these methods but did not meet the time-restricted definition of clustering. Using this time-restricted definition allowed us to classify cases occurring between 1997 and 2003 (for which we had data on the genotypes of isolates collected in the previous year) but not cases occurring in 1996; therefore, results of all analyses using time-restricted clustering data are presented for cases occurring between 1997 and 2003. Confidence intervals for yearly TB case rates were generated assuming a Poisson distribution, using the method described by Buchanan (28).

RESULTS

Demographic data

In 2000, the population of Arkansas was 2,673,400 (19). This population is largely rural: In 2000, 49.5 percent of the population lived in a county falling within an MSA, while 50.5 percent lived in non-MSA counties (19). Foreign-born persons, who make up 11.1 percent of the US population, made up 2.8 percent of the population of Arkansas in 2000. The population was 77.8 percent non-Hispanic White, 15.7 percent non-Hispanic Black, 4.7 percent Hispanic/Latino, 1.1 percent Asian/Pacific Islander, and 0.7 percent American Indian/Alaskan Native (19).

TB cases

Of the 1,402 cases of TB reported in Arkansas between 1996 and 2003, 690 patients (49.2 percent) were non-Hispanic White, 483 (34.5 percent) were non-Hispanic Black, 118 (8.4 percent) were Hispanic, 103 (7.4 percent) were Asian/Pacific Islander, and six (0.4 percent) were American Indian/Alaskan Native. Race/ethnicity was unknown for two cases (0.1 percent). Human immunodeficiency virus status was known for 766 patients (54.6 percent), and of these patients, 52 (6.8 percent) were human immunodeficiency virus-positive. With regard to urbanicity, 632 patients (45.1 percent) resided in an MSA, and 770 (54.9 percent) resided outside of any MSA.

Genotype patterns and clustering of isolates

Using the conventional cluster definition, 532 of 997 cases (53.4 percent) were clustered with at least one other case in the population, resulting in 113 clusters. Thirty-four (30 percent) of these clusters were defined on the basis of identical IS6110 fingerprints with fewer than six bands along with identical spoligotypes, while 79 (70 percent) were defined on the basis of six or more IS6110 bands that were identical or that differed by one band but had identical spoligotype patterns. The sizes of the clusters ranged from two isolates, accounting for 57 clusters (50.4 percent), to 35 isolates (one cluster). The time spans of individual clusters ranged from 1 year to the full 8 years of the study period.

Of the 532 isolates clustered by conventional methods, 309 matched the isolate of a case that was diagnosed within the same 1-year period and were thus considered clustered by our time-restricted cluster definition.
Incidence trends

The incidence of culture-confirmed TB in Arkansas declined by 2.7 cases per 100,000 population between 1997 and 2003 (figure 1). This overall decline resulted from a decline in both clustered cases, which declined by 1.0 case per 100,000, and nonclustered cases, which declined by 1.7 cases per 100,000.

In the age group 20–64 years, the overall incidence of culture-confirmed TB declined by 1.5 cases per 100,000, and the absolute declines in nonclustered and clustered cases were identical at 1.0 case per 100,000 for each (figure 2, top). The largest decline in the incidence of TB occurred among persons aged 65 years or older, with an absolute decline between 1997 and 2003 of 11.4 cases per 100,000 (figure 2, bottom). The absolute decline of nonclustered cases was 1.8 times the absolute decline of the clustered cases.

The incidence of culture-confirmed TB was consistently higher in Blacks than in Whites (figure 3), but Blacks also experienced the greatest decline in incidence. Among Blacks, incidence declined by 7.3 cases per 100,000, and the absolute declines in nonclustered and clustered cases were identical at 1.0 case per 100,000 for each (figure 2, top). The largest decline in the incidence of TB occurred among persons aged 65 years or older, with an absolute decline between 1997 and 2003 of 11.4 cases per 100,000 (figure 2, bottom). The absolute decline of nonclustered cases was 1.8 times the absolute decline of the clustered cases.

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### DISCUSSION

We used molecular genotyping data to estimate the relative contributions of recent and remotely acquired infections to the yearly incidence of TB in Arkansas. Our analysis indicated that the decline in the incidence of TB in Arkansas between 1997 and 2003 was most likely due to a decline in the incidence of reactivated latent infections among persons aged 65 years or more. This decline was primarily seen in Blacks and was most prominent in rural areas of the state.

The steep decline in reactivation cases in the oldest age group (≥65 years) and the minimal decline in reactivation cases among persons aged 20–64 years suggests that a cohort effect may be responsible for most of the decreased incidence of TB in Arkansas. With a steep decline in TB incidence in Arkansas (as well as the United States generally) in the first half of the 20th century, each successive birth cohort was exposed to a lower risk of infection with *M. tuberculosis*. As a result, the prevalence of latent TB infection is highest in the oldest persons in the population and decreases with decreasing age. The declining incidence of TB in the population may reflect earlier birth cohorts’ leaving the population as more recent birth cohorts enter it. This is similar to what has been reported in the Netherlands.

### TABLE 2. Distribution of previously identified risk factors for clustering among tuberculosis cases clustered within a 1-year time interval and tuberculosis cases clustered with more than 1 year between clustered cases, Arkansas, 1997–2003

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cases clustered within 1 year</th>
<th>Cases clustered outside 1 year</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with risk factor</td>
<td>No. of isolates</td>
<td>%</td>
</tr>
<tr>
<td>Non-Hispanic Black race/ethnicity</td>
<td>145</td>
<td>309</td>
<td>46.9</td>
</tr>
<tr>
<td>Positive sputum smear</td>
<td>126</td>
<td>309</td>
<td>40.8</td>
</tr>
<tr>
<td>Cavitary disease</td>
<td>113</td>
<td>275</td>
<td>41.1</td>
</tr>
<tr>
<td>Positive for human immunodeficiency virus</td>
<td>18</td>
<td>211</td>
<td>8.5</td>
</tr>
<tr>
<td>Homeless</td>
<td>15</td>
<td>307</td>
<td>4.9</td>
</tr>
<tr>
<td>Excessive alcohol use</td>
<td>64</td>
<td>229</td>
<td>27.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>208</td>
<td>309</td>
<td>67.3</td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td>2</td>
<td>204</td>
<td>1.0</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>94</td>
<td>309</td>
<td>30.4</td>
</tr>
</tbody>
</table>

* Two-sided p value from a chi-squared test comparing risk factor frequencies between cases clustered within 1 year and cases clustered with more than 1 year between clustered cases.
the Dutch population also experienced a steep decline in TB incidence early in the 20th century (11).

The marked decline in the incidence of TB in non-Hispanic Blacks is a welcome finding. In the United States, the burden of disease has weighed disproportionately on this group, with TB incidence being eight times higher than that seen in non-Hispanic Whites in 2002 (13). However, this decline does not appear to be the result of reduced transmission in this population—the incidence of clustered cases declined minimally during the study period. Rather, a decline in the incidence of reactivated latent infections is driving this trend. While the numbers in our study were too low to stratify racial/ethnic groups by age, the race/ethnicity-stratified yearly incidences of nonclustered cases suggested that the cohort effect is predominately seen in the non-Hispanic Black population, because the incidence of reactivated TB in non-Hispanic Blacks declined steeply while declining minimally in non-Hispanic Whites.

Molecular epidemiologic investigations have consistently identified non-Hispanic Black race/ethnicity as a risk factor for molecular clustering (9, 29, 30). It has been suggested that higher frequencies of excessive alcohol use, drug use, incarceration, and infection with human immunodeficiency virus—all identified risk factors for clustering—may be responsible for the higher rates of TB seen among non-Hispanic Blacks (29). While not discounting the importance of known risk factors, our results suggest that in Arkansas, the higher rates of TB currently observed in non-Hispanic Blacks are as much the result of historical trends as of contemporary risk behaviors. Historically, the incidence of TB has been higher in Blacks than in Whites, in both Arkansas and the United States as a whole. Because active TB can result from infection acquired many years or even decades in the past, the legacy of historical TB transmission may be felt in a population for generations. Similarly, reductions in transmission will continue to have effects on overall disease incidence for many years.

The complex pathogenesis of TB makes the evaluation of TB control programs difficult. For many decades, Arkansas has had a strong TB control program that rapidly identifies and promptly tests infectious cases, achieving a 98 percent cure rate year after year. Latent infection among contacts is particularly sought out and treated. With currently available data, however, it is impossible to disentangle the effect of a strong TB control program from what appears to be a strong cohort effect. While our analysis suggests a large role for historical forces in driving recent trends, the consistently low level of active transmission, as well as the low incidence of multiple-drug-resistant TB in this population (12–18, 20), reflects favorably on Arkansas’ TB control program. Evaluating the effectiveness of control programs in the context of larger secular trends is far from straightforward, and this is an area that warrants further exploration.

Arkansas differs from the rest of the United States, particularly from the urban areas in which molecular typing for TB has been validated as a measure of recent transmission. In the United States, the foreign-born population suffers a disproportionate burden of TB. However, in Arkansas, the foreign-born population is small (2.8 percent), and cases in foreign-born persons represent only a small proportion (4.4 percent) of all reported TB cases. Additionally, while the majority of the US population lives in urban areas, only a minority of the population of Arkansas does. The pattern of TB incidence also differs. In urban areas of the United States,
the incidence of TB was 24 percent higher than the national rate in 2003 (12), while during the same year in Arkansas, the incidence of TB was 23 percent higher in rural areas than in the state overall. Because the bulk of Arkansas’ population resides in rural counties, the decline in the incidence of TB in these counties between 1997 and 2003 appears to be a key driver of the overall decline in TB in Arkansas.

Our results differ from those of a previous investigation conducted in San Francisco, California, by Jasmer et al. (10). They concluded that the decline in TB incidence in that population between 1991 and 1997 was due primarily to a decline in active transmission. It is not surprising that similar analyses of two very different populations found divergent results: Transmission dynamics in the rural, highly stable population of Arkansas are probably quite different from those in a diverse urban population like San Francisco’s. The molecular typing methods we used differed slightly from those of the San Francisco study (we used spoligotyping as a secondary typing method, which is somewhat less discriminatory than the pTBN12 typing method (31) used by Jasmer et al. (10)), and this may have resulted in an overestimate of the amount of clustering, particularly.
among isolates with fewer than six IS610 bands. However, in a time-trends analysis of our study sample that was restricted to isolates with six or more IS610 bands, trends over time matched those seen in our full study set (data not shown). Therefore, we find it unlikely that this methodological difference resulted in the distinct time trends identified in our respective study populations.

The method of “clustering” cases that exhibit identical or similar DNA fingerprint patterns to measure recent transmission has been used most widely in diverse, urban populations. Of the limited number of studies that have attempted to validate this approach against epidemiologic data, the majority have been conducted in urban populations (6, 32). In rural, stable populations, the predictive value of clustering for recent transmission may be lower, since clusters may include patients between whom transmission occurred in the remote past (24, 25, 33).

By restricting our definition of clustering to cases with matching fingerprints that were diagnosed within 1 year of one another, we attempted to increase the specificity of this measure for recent transmission. While cases meeting our time-restricted clustering definition were more likely to

FIGURE 3. Incidence of culture-confirmed, nonclustered, and clustered cases of tuberculosis among non-Hispanic Whites (top) and non-Hispanic Blacks (bottom) in Arkansas, using the time-restricted definition of clustering, 1997–2003. A case was considered part of a time-restricted cluster if it was clustered by the conventional definition, using IS610 restriction fragment length polymorphism and spoligotyping, with another isolate diagnosed within the 1-year period prior to its diagnosis date. Bars, 95% confidence interval.
involve known risk factors for recent TB transmission than were clustered cases that did not meet the time restriction, we cannot conclude that our restricted definition is more specific for recent transmission without epidemiologic contact-tracing data with which to verify transmission links.

This potential misclassification and differences between the demographic characteristics of patients with genotyped isolates and those of patients without genotyped isolates present potential sources of bias in our study sample. However, we have no reason to believe that misclassification differed between years in our study, and we are confident in using these tools to follow trends over time. Additionally, the subpopulations for which we were less likely to have genotyped isolates (Asian/Pacific Islanders, Hispanics, foreign-born persons, and persons under age 20 years) represented only a small proportion of our study population; for that reason, we did not attempt to draw inferences about these groups. We are confident that, despite these potential limitations, our study methods allowed us to detect important factors driving trends in TB in Arkansas.

Effective TB control programs are essential for reaching the goal of TB elimination in the United States. Our results suggest that the decline in active transmission of *M. tuberculosis* infection observed in Arkansas between 1997 and 2003 was not as important as the decline in the rate of reactivated latent infection during the same period. These results emphasize the need to reduce the reservoir of latent infections in order to continue to produce long-term declines.

**FIGURE 4.** Incidence of culture-confirmed, nonclustered, and clustered cases of tuberculosis in rural counties (top) and urban counties (bottom) in Arkansas, using the time-restricted clustering definition, 1997–2003. A case was considered part of a time-restricted cluster if it was clustered by the conventional definition, using IS6110 restriction fragment length polymorphism and spoligotyping, with another isolate diagnosed within the 1-year period prior to its diagnosis date. Bars, 95% confidence interval.
in the overall incidence of TB. Of particular concern are subpopulations in which the incidence of disease due to recently acquired infection remains stable—without reducing the level of active transmission and therefore the risk of becoming latently infected, we can expect declines in the overall incidence of TB in these populations to eventually level off. In order to reach TB elimination goals, improvements in the effective identification and interruption of actively transmitted cases are essential.

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Conflict of interest: none declared.

REFERENCES


