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Seasonal variation among tuberculosis suspects in four countries

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Summary The objective of the study was to analyze monthly trends across a calendar year in tuberculosis suspects and sputum smear-positive cases based on nationally representative samples of tuberculosis laboratory registers from Moldova, Mongolia, Uganda and Zimbabwe. Out of the 47 140 suspects registered in the tuberculosis laboratory registers, 13.4% (6312) were cases. The proportion varied from country to country, Moldova having the lowest (9%) and Uganda the highest (21%). From the monthly proportion of suspects and cases among total suspects and cases, seasonal variations were most marked in Mongolia which, among the four countries, also has the most pronounced seasonal variation in ambient temperature. Female suspects were consistently older than female cases in all four countries. Among males, male suspects were almost consistently older than male cases, most consistently in Moldova. Seasons seem to affect attendance to diagnostic laboratory services, evidenced by the contrasting findings of Mongolia (extreme continental northern climate) compared to Uganda (equatorial climate). A combination of external and possibly endogenous factors seems to determine whether tuberculosis suspects and cases present themselves to health care facilities.

1. Introduction

Trends and seasonal variations of tuberculosis have been demonstrated in a number of studies in different countries with reported peaks in late winter and early spring or summer.[1–9] Much less is known about such variations among patients presenting as tuberculosis suspects as, in contrast to morbidity data, such information is virtually

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never routinely accessible to national health authorities. The objective of this study was therefore to analyze monthly trends across a calendar year in tuberculosis suspects and sputum smear-positive cases amongst them, based on nationally representative samples of tuberculosis laboratory registers from Moldova, Mongolia, Uganda and Zimbabwe.

2. Materials and methods

A retrospective, record-based study, utilizing information routinely available in national TB control services was carried out. Records of examinees in the Tuberculosis Laboratory Register from at least one calendar year during the period January 1999—December 2003 were utilized for

Table 1 Tuberculosis suspects and cases, by month and country.

Month	Moldova (2003)		Mongolia (2003)		Uganda (2001)		Zimbabwe (2002)		Total	
	Suspects	Cases	Suspects	Cases	Suspects	Cases	Suspects	Cases	Suspects	Cases
Jan	890	92	1069	121	668	150	1374	207	4001	570
Feb	1054	92	1196	153	526	114	1258	182	4034	541
Mar	1121	66	1380	158	674	149	1395	143	4570	516
Apr	877	66	1399	160	629	105	1320	172	4225	503
May	760	80	1141	140	631	136	1294	199	3826	555
Jun	891	94	1166	168	583	131	1120	139	3760	532
Jul	899	73	907	135	715	132	1391	164	3912	504
Aug	720	68	769	98	682	134	1450	168	3621	468
Sep	705	75	916	96	627	126	1381	237	3629	534
Oct	953	93	894	92	590	126	1537	241	3974	552
Nov	916	89	912	83	727	161	1356	227	3911	560
Dec	1068	97	933	91	604	134	1072	155	3677	477
Total	10854	985	12682	1495	7656	1598	15948	2234	47140	6312

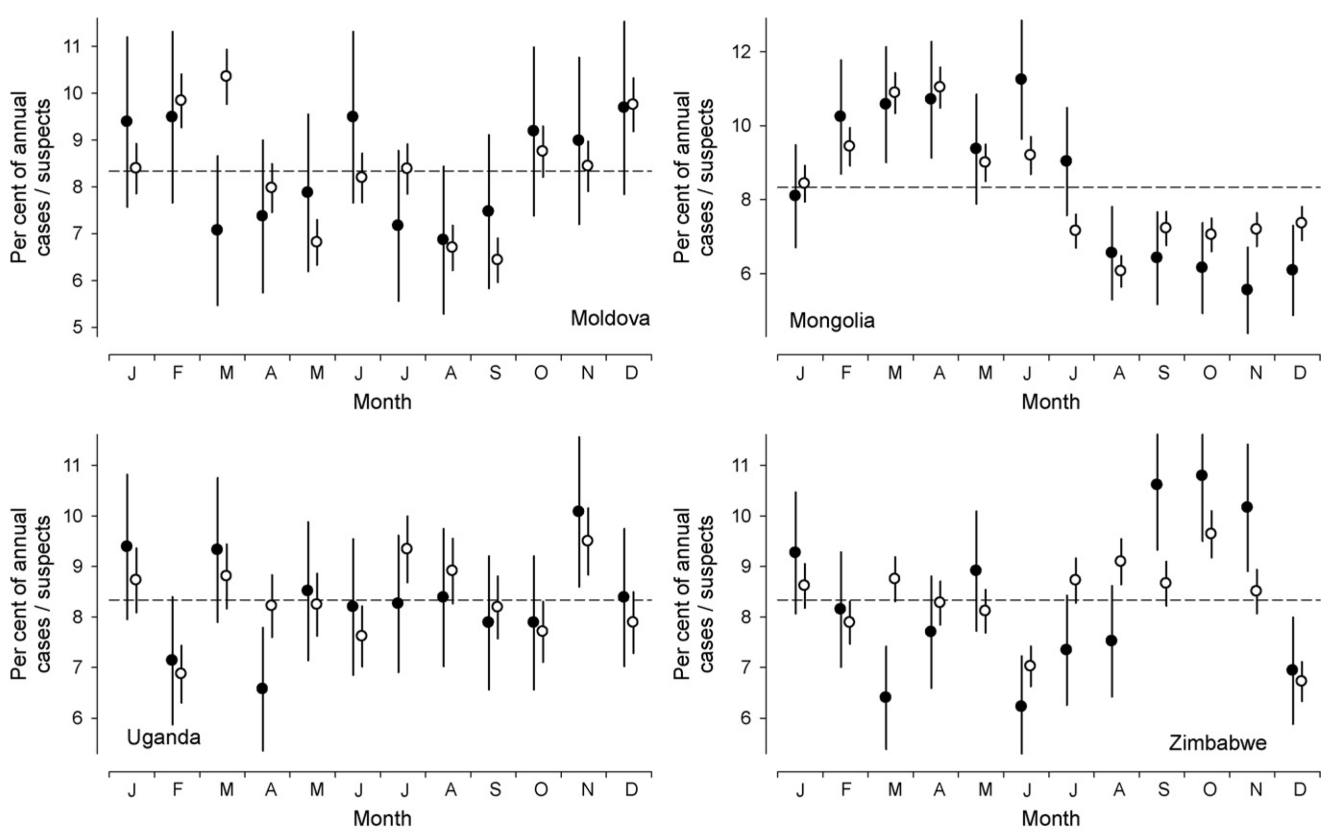

Figure 1 Monthly proportion of suspects and cases among total suspects and cases respectively (●cases ○suspects)
Brief description: From the monthly proportion of suspects and cases among total suspects and cases, seasonal variations are most marked in Mongolia which, among the four countries, also has the most pronounced seasonal variation in ambient temperature.

the study in Moldova, Mongolia, Uganda and Zimbabwe. From lists of laboratories that offered tuberculosis diagnostic services using sputum smear microscopy and used a standard Tuberculosis Laboratory Register, 23 in Moldova, all 31 in Mongolia, 30 in Uganda and 23 in Zimbabwe were randomly selected to ensure the desired unbiased and representative evaluation of the work in the countries' laboratories. Permission to carry out the study was granted by the departments of health in the respective countries.

2.1. Data collection, entry, validation and analysis

From these 107 laboratories, relevant data were electronically captured from the registers and validated by double entry and comparison, and, where indicated, were corrected by rectifying identified discordances made during data entry against the physical registers. A uniform data entry form was used by all four countries using the freely available EpiData Entry software (version 3.1, EpiData Association, Odense, Denmark). Details of these procedures have been reported elsewhere.[10–13] The validated files from the laboratories were combined for analysis. Analysis was performed using EpiData Analysis (version 2.0, EpiData Association, Odense, Denmark). In order to analyse the pattern in a calendar year, as unbiased as possible a selection was necessary, but difficult to achieve. Laboratories that had months with no examinations or <5% of monthly average examinees over the complete study period were excluded. The year during the study period for which sputum examination in all the 12 months was available was selected for each country. The proportion of patients defined as tuberculosis cases among tuberculosis suspects was determined. For the purpose of the study, a case of smear-positive tuberculosis was defined as a suspect with at least one acid-fast bacillus (AFB) in at least one of the serial examinations. Analyses included univariate and stratified description of sex and age among both suspects and cases.

3. Results

Out of a total of 130 311 records from 107 laboratories in the four countries, 1503 (1.2%) records were excluded because of improper recording practices i.e. 'No result recorded' followed by a valid result recorded. Eighty-two laboratories (Moldova — 16, Mongolia — 25, Uganda — 24, and Zimbabwe — 17) with a total of 77 506 records met the primary criterion of continuous recording of examinees during every month throughout the selected year. Of the 77 506 records, 23 844 examinees other than suspects (19 539 with a follow-up examination and 4305 with unknown reason for examina-

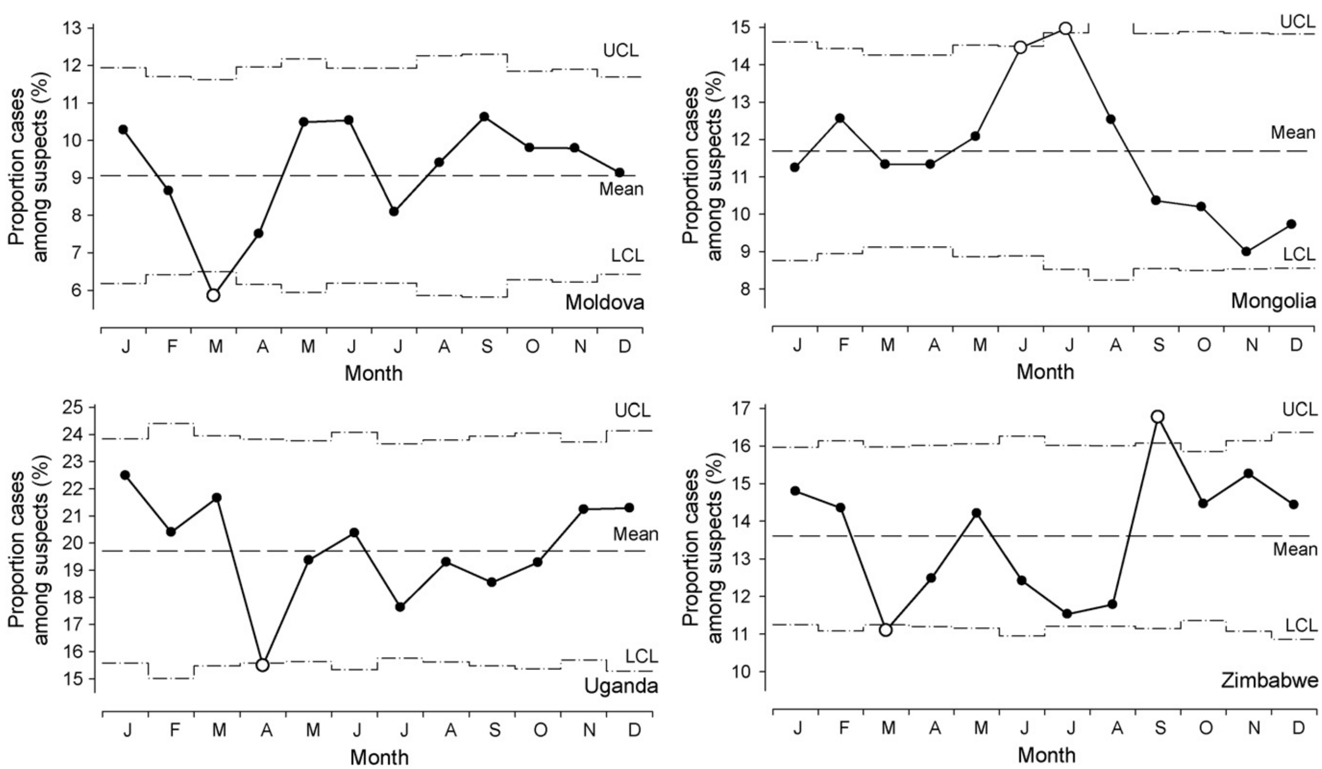

Figure 2 Proportion of cases among suspects by month (UCL: upper control limit; LCL: lower control limit)
Brief description: Statistical process control charts were used to summarize variation and uncertainty in the monthly proportions of cases among suspects in the four countries. In Mongolia, these proportions show a definite excess proportion of cases among suspects in June and July, followed by a considerable decline to below average proportions from August through December. Lower than expected proportions were found in March in Moldova and Zimbabwe and in April in Uganda, while a higher than expected prevalence was recorded in September in Zimbabwe.

tion) were excluded. Among the remaining suspects, 6177 with unknown age and 345 with unknown gender were also excluded from further analysis. The remaining 47 140 suspects were included in the analysis. The distribution by month and country of these and the 6312 (13.4%) cases among them is shown in Table 1.

3.1. Monthly distribution of suspects and cases

From the monthly proportion of suspects and cases among total suspects and cases (Figure 1), seasonal variations are most marked in Mongolia which, among the four countries, also has the most pronounced seasonal variation in ambient temperature. From August through December, both suspects and cases were markedly below, and from February through June markedly above, the annual average. Surface temperature in Mongolia follows the pattern of the northern hemisphere with a trough in January and a peak in July. The number of suspects and cases was high during the months February through June with a peak for the cases in June (warmest months: April to September with a peak temperature in July[14]). While also in the northern hemisphere, the pattern in Moldova differs importantly from that observed in Mongolia: the largest proportion of annual suspects was seen in March when the contribution to annual cases was lowest. The proportion of cases was above average from October through February, and briefly in July. In Uganda, an equatorial country, tuberculosis suspects and cases were evenly distributed throughout the year. It is nevertheless notable that the contribution of suspects and cases to the annual total was lower in December than in January. In Zimbabwe, located in the southern hemisphere, there is a marked increase in the number in late spring (September—October. October is the hottest month whilst July is the coldest). Even more pronounced than in Uganda, the monthly contribution to the annual total of cases and suspects in December was notably lower than in January.

3.2. Prevalence of smear positive cases among suspects

Out of the 47 140 suspects, 13.4% (6312) were cases. The proportion varied from country to country, Moldova having the lowest (9%) and Uganda the highest proportion (21%) as shown in Table 1. Statistical process control charts were used to summarize variation and uncertainty in the monthly proportions of cases among suspects in the four countries (Figure 2). In Mongolia, these proportions show a definite excess proportion of cases among suspects in June and July, followed by a considerable decline to below average proportions from August through December. Lower than expected proportions were found in March in Moldova and Zimbabwe and in April in Uganda, while a higher than expected prevalence was recorded in September in Zimbabwe. Nevertheless, apart from these latter deviations from the average, the possible relation to season is evident only in Mongolia.

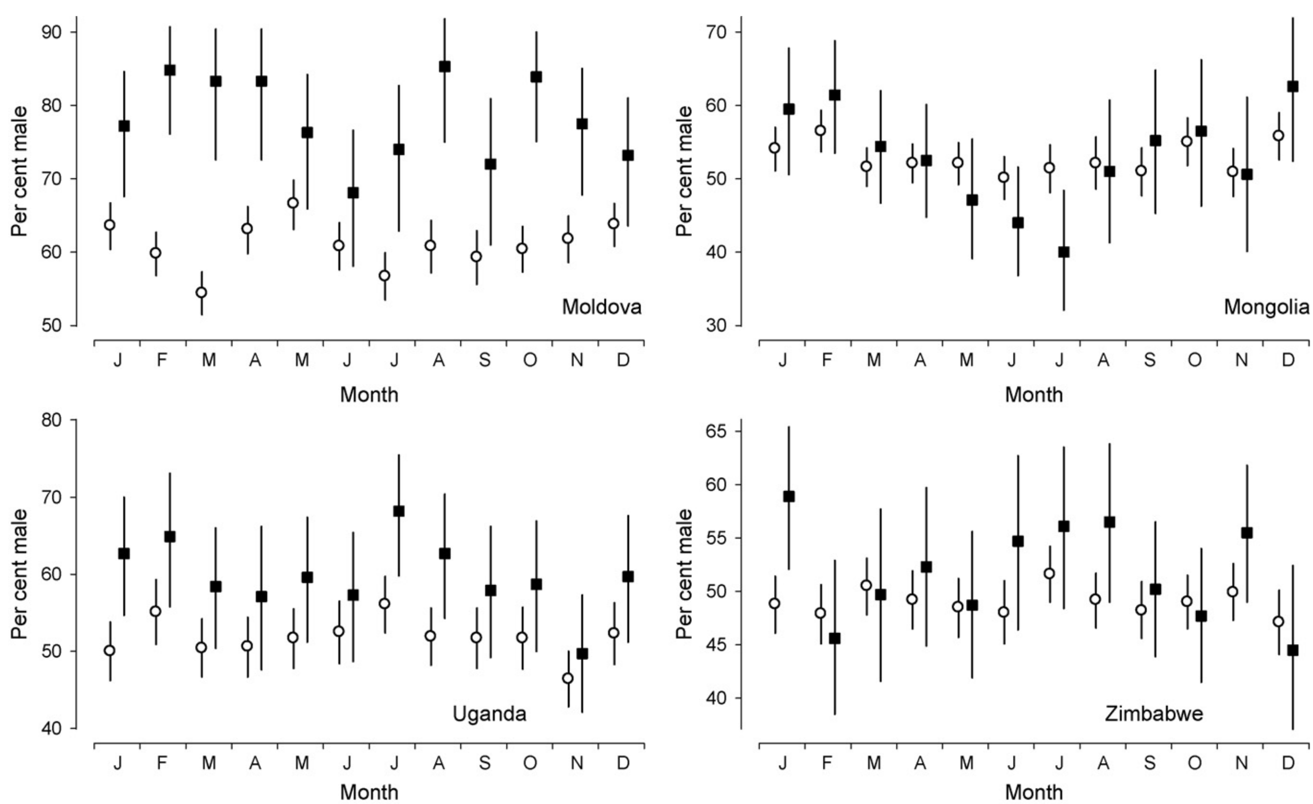

Figure 3 Proportion of males among suspects and cases by month (○suspects ■cases)
Brief description: In three countries, there were more males than females among suspects and cases. In all four countries, males were more likely to be cases than suspects, but the male-to-female case-to-suspect ratio was most pronounced in Moldova.

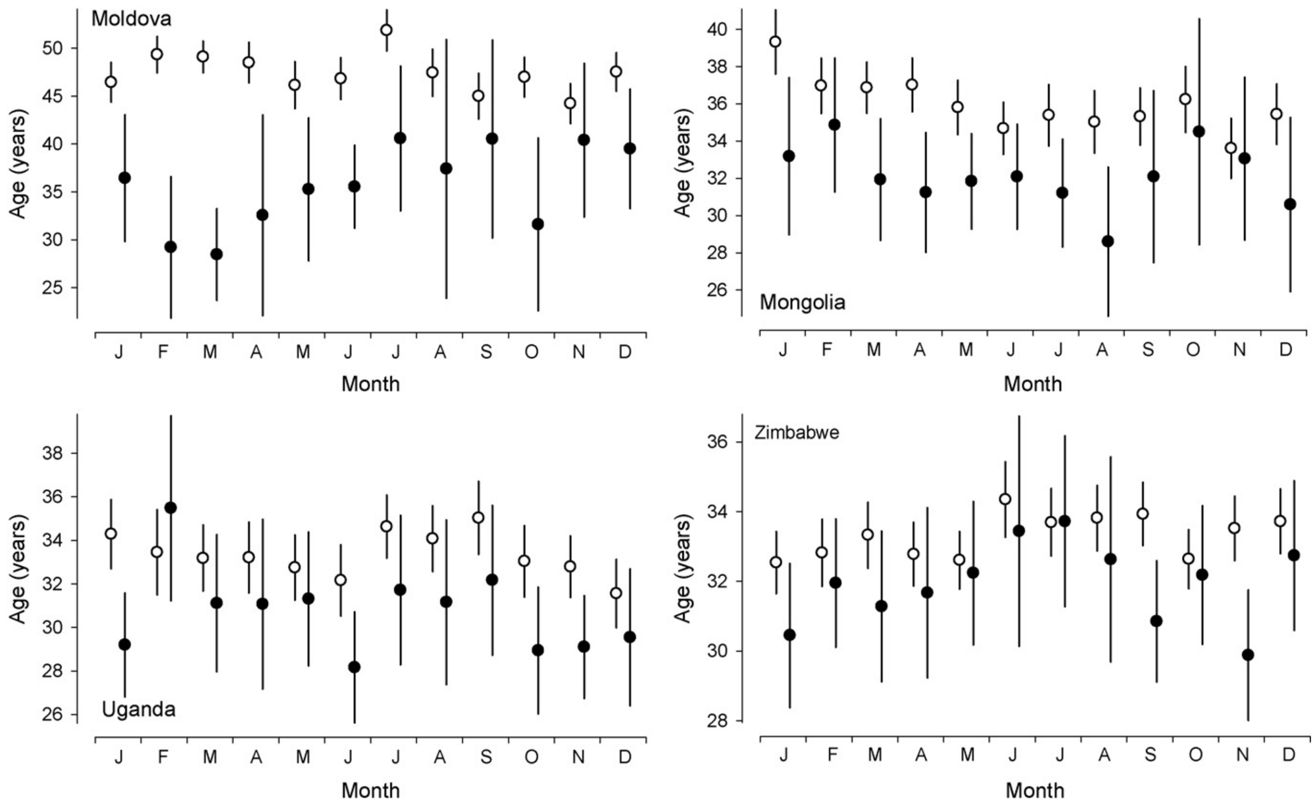

Figure 4 Mean age and 95% confidence interval among female suspects and cases by month (○suspects ●cases)
Brief description: Female suspects were consistently older than female cases in all four countries. In Moldova, female suspects were aged on average about 45 to 50 years, with little change throughout the year. In contrast, the mean age among female cases changed importantly over the course of a year, case patients tending to be youngest in the early part of the year and oldest in the second half.

3.3. Proportion of males among suspects and cases

In three countries, there were more males than females among tuberculosis suspects and cases (Figure 3). The proportion of males among suspects was respectively 60.8%, 52.7%, 51.6%, and 49.0% in Moldova, Mongolia, Uganda, and Zimbabwe. The respective proportions among cases were 78.0%, 52.4%, 59.6%, and 51.7%. Thus, in all four countries, males were more likely to be cases than suspects, but the male-to-female case-to-suspect ratio was most pronounced in Moldova. The course over the year in the proportions of males among suspects and cases was most distinct when comparing Moldova and Mongolia. In Mongolia, males contributed 60% and more from December through February, but only around 40% in July. The seasonal course was the same among suspects, but the amplitude was by far smaller. In contrast, in Moldova, the proportion of males among suspects appeared to drift apart from that among cases in spring and autumn. In Uganda and Zimbabwe, the fluctuations in the proportion of males were much less pronounced and were more or less in parallel among cases and suspects.

3.4. Age distribution by gender

Female suspects were consistently older than female cases in all four countries (Figure 4). In Moldova, female suspects were aged on average about 45 to 50 years, with little change throughout the year. In contrast, the mean age among female cases changed importantly over the course of a year, case patients tending to be youngest in the early part of the year and oldest in the second half. In Mongolia, there were fluctuations in age among females but cases more or less followed the pattern among suspects. In Uganda, no clear pattern emerged, while in Zimbabwe, there was a suggestion of an increase in the age of females towards the middle of the year, particularly among the cases. Among males, suspects were almost consistently older than cases, most consistently in Moldova (Figure 5). No clear seasonal pattern emerged in any of the four countries, neither among cases nor among suspects.

4. Discussion

While notifications of tuberculosis might not be much biased by calendar time, individual laboratories are much more prone to become operationally defunct through vacation, illness or lack of supplies at any given time during a year. For the purpose of this study it was thus required that laboratory records demonstrated that work was actually done in every single month at least at some arbitrarily chosen minimum level. Because there was no criterion that could reasonably define uninterrupted work, a certain bias was undoubtedly introduced in the current analysis. Nevertheless, some striking findings in some of the countries examined here

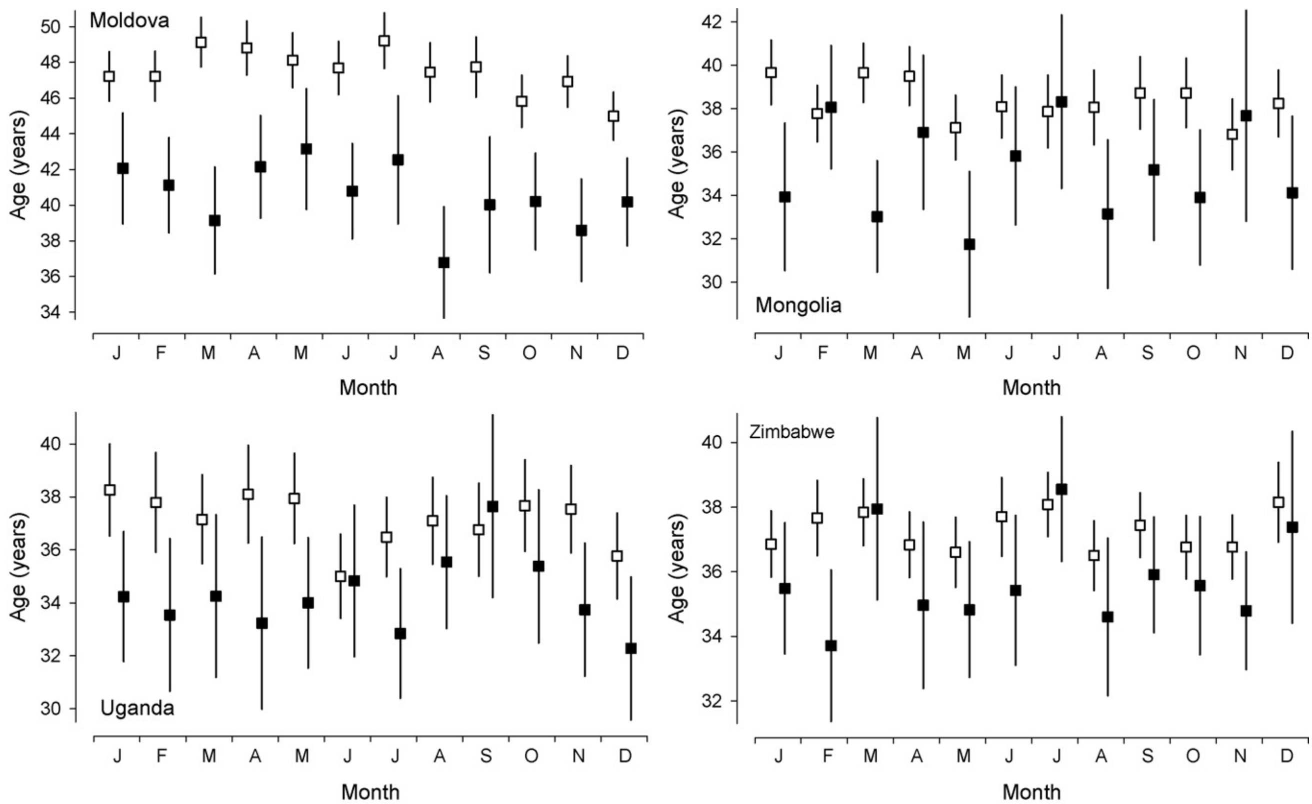

Figure 5 Mean age and 95% confidence interval among male suspects and cases by month (□suspects ■cases)
Brief description: Among males, suspects were almost consistently older than cases, most consistently in Moldova. No clear seasonal pattern emerged in any of the four countries, neither among cases nor among suspects.

would suggest a pertinent role of seasons on the work performed in peripheral sputum smear microscopy laboratories. To impute such an influence is particularly suggestive in an analysis of age and gender of examinees which is least likely affected by the staffing and performance of the laboratory.

A number of studies[1–7] have shown seasonal variation in trends of tuberculosis. Seasons exert external influences but also result in modification of endogenous factors. Externally, seasons and weather influence human behavior. In the colder seasons people tend to stay indoors, leading to prolonged exposure time to patients with transmissible pulmonary tuberculosis, and resulting more frequently in successful transmission. Adverse weather may not only force people to spend more time indoors, but may also hamper accessibility to health care facilities. Endogenously, the role of vitamin D deficiency has been espoused as a possible explanation for an increased risk for progression to disease, and such deficiencies might be seasonal in areas with a long cold season like Mongolia, resulting in deficient monocyte and macrophage function (cellular immunity), leading to reactivation of dormant mycobacterial infection.[15,16]

In our study, there was a marked decrease in the number of suspects and cases during the coldest months in Mongolia (October—March) and Zimbabwe (May—July). In Moldova the number of cases peaked during cold months (October—March), but there is a sustained decline in both the number of suspects and cases during the months of July to September. During this period, schools are closed and it is the peak harvesting period when people are busy in their fields before the onset of winter. Fewer people might visit health facilities during this period. Of interest to note also is the decline in the number of suspects and cases in December in Uganda and Zimbabwe. This might be attributed to health—seeking behavior because of the festive (Christmas) season. Most of the health care workers go on leave and most people visit relatives in the countryside. So, fewer people visit health facilities during this time of the year. There were no obvious variations in the pattern in Uganda. This is remarkable and might be seen in the context that Uganda lies in the Equatorial region and is warm throughout the year.

A simple way of presenting information on laboratory yield is to plot the monthly proportion of tuberculosis cases among suspects. This would be useful for both the technicians, clinicians and managers to detect deviations from the expected and take corrective measures. For the proportion of cases among suspects (Figure 2), the trend shows below mean levels in winter and early spring in Mongolia and Zimbabwe. The proportion of smear-positive tuberculosis cases among suspects was 13.4%, ranging from the lowest with 9% in Moldova to the highest with 21% in Uganda. In countries where there is no other very frequent cause of chronic cough, the prevalence may frequently be between 5 and 20% if tuberculosis is common and resources are limited. Higher proportions are often encountered in situations where there is a delay in diagnosis due to patients' health-seeking behaviour or a low index of suspicion on the part of clinicians. The clinicians may also be applying too strict criteria for screening, resulting in referral to bacteriologic examination of only those with blatantly suggestive signs and symptoms of possible tuberculosis. Too low proportions would occur in settings where there is a too permissive selection of suspects i.e. ordering sputum smear examinations in individuals with a cough of very short duration. A strategy of active case-detection would result in the same discouragingly low positivity frequencies[17].

Overall there were more males than females both among the suspects and cases. In Mongolia, there was marked change in the proportion of genders over the year. In that country, these proportions ran almost parallel among both tuberculosis suspects and cases, while in Moldova, the proportional contributions tended to drift apart among suspects compared to cases. A number of studies in various countries have shown that tuberculosis is diagnosed more in males than females.[18–23] Gender differences may be explained in terms of differences in exposure as a result of different social roles[24] and responsibilities between men and women. Access to healthcare services might also explain the differences even though this is difficult to assess. While it is quite suggestive that seasons have a remarkable, though rather different, effect on the gender split of tuberculosis suspects and cases in Moldova and Mongolia, it remains speculative as to the reason why this would be the case.

Among both suspects and cases, males were older than females; the cases were younger than the suspects. The age difference between the cases and suspects over the months was most marked in Moldova and Mongolia. Why the age of female tuberculosis suspects remained relatively unchanged but markedly changed among female cases in Moldova, and other fluctuations that were observed remains, however, elusive. The ratio of the recently to remotely infected is likely to be highest among the youngest and to be decreasing with age. Nevertheless, with increasing age, remotely acquired infections will also increasingly be eliminated. To what extent the observed seasonal fluctuations in the age of tuberculosis cases reflects reactivation or direct progression from recently acquired infection cannot be answered by this study.

This study demonstrates that seasons seem to affect attendance to diagnostic laboratory services, evidenced by the contrasting findings of Mongolia (extreme continental northern climate) compared to Uganda (equatorial climate). In some poorly understood ways, a combination of external and possibly endogenous factors seems to determine whether tuberculosis suspects and cases present themselves to health care facilities.

Authors' contributions: AK, BM, DL, HLR and NN designed the study protocol.

AK, BM, DL and NN collected data from the laboratories.

AK, BM, DL, HLR, JL and NN carried out data analysis and interpretation.

BM and HLR drafted the manuscript.

All authors revised the manuscript and made contributions, read and approved the final manuscript.

HLR is the guarantor of the paper.

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Conflicts of interest: None declared.

Ethical approval: Not required.

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