A fourteen-year follow-up of ultrasound-detected urinary tract pathology associated with urogenital schistosomiasis in women living in the Msambweni region of coastal Kenya

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ABSTRACT

Background: Complications of urogenital schistosomiasis include acute inflammatory and then chronic fibrotic changes within the urogenital tract. Disease burden of this neglected tropical disease is often underestimated, as only active, urine egg-patent *Schistosoma* infection is formally considered. Previous studies have focussed on short-term effects of praziquantel treatment on urinary tract pathology, demonstrating that acute inflammation is reversible. However, the reversibility of chronic changes is less well studied.

Methods: Our study compared, at two time points 14 years apart, urine egg-patent infection and urinary tract pathology in a cohort of women living in a highly endemic area having intermittent praziquantel treatment(s). In 2014, we matched 93 women to their findings in a previous study in 2000.

Results: Between 2000 and 2014 the rate of egg-patent infection decreased from 34% (95% CI 25-44%) to 9% (95% CI 3-14). However, urinary tract pathology increased from 15% (95% CI 8-22) to 19% (95% CI 11-27), with the greatest increase seen in bladder thickening and shape abnormality.

Conclusions: Despite praziquantel treatment, fibrosis from chronic schistosomiasis outlasts the presence of active infection, continuing to cause lasting morbidity. We suggest that future efforts to eliminate persistent morbidity attributable to schistosomiasis should include better intensified disease management.

Key words: Schistosomiasis, *Schistosoma haematobium*, Ultrasonography, Urogenital Diseases

INTRODUCTION

Schistosomiasis continues to be the one of the world's most prevalent parasitic diseases, with an estimated 700 million people at risk and 251 million requiring preventative treatment in 2021.[1] Currently sanctioned schistosomiasis surveillance (based on microscopic egg detection) accounts for those with active infection, but does not include all those with the persistent sequelae that follow from repeated or prolonged infection(s). Recently, there has been a redirection of schistosomiasis morbidity control away from a focus only on infection rates to instead consider the long-lasting morbidity associated with the disease, including the post-infection period(s). Although global burden of schistosomiasis-related disease is currently estimated to be 1.4 million disability-adjusted life-years (DALYs) based on active infection prevalence,[2] its burden could be as high as 56 million DALYs when longstanding morbidity is taken into consideration.[3]

Human infection by the waterborne trematode parasite *Schistosoma (S.) haematobium* causes localised damage to the urinary system and genital tract,[4] as well as systemic manifestations such as anaemia, growth stunting, and issues affecting women's and men's sexual and reproductive health.[5] Hosts become infected through contact with schistosome cercariae found in snail-infested fresh water bodies. Adult trematode pairs can release thousands of eggs which are excreted through the host's urinary tract. However, only about half the parasite eggs leave the human body. Pathological changes occur due to the host's immune response to trapped schistosome eggs that remain lodged in the walls of the urinary tract. A polarised T helper cell type 2 (Th2) response initiated by schistosome soluble egg antigen causes an influx of inflammatory cells such as eosinophils, monocytes, fibroblasts, and mast cells into the

local area.[6] Granulation tissue and scarring then forms around trapped eggs in order to prevent further localised egg-induced damage.[7] At this stage, *S. haematobium*-associated inflammation can cause bladder changes, including masses and ulceration, which may manifest as pain, dysuria, and haematuria.[4, 8] Immunoregulation during chronic infection can eventually lead to a dampening (modulation) of the host's immune response, but can meanwhile leave irreversible fibrosis and calcification of the bladder wall or distal ureters. In severe cases, this thickening can lead to ureteric dilatation and renal obstruction as late signs of pathology.[9, 10] Life-threatening pathology such as renal failure or squamous cell carcinoma of the bladder develops in around 1% of individuals in highly-endemic settings.[11]

The introduction of portable ultrasound imaging has increased our understanding of the evolution of organ specific pathology in schistosomiasis.[12, 13] In an attempt to standardise the reporting of pathological changes, the World Health Organization (WHO) has produced a practical guide to ultrasound assessment of both intestinal and urogenital schistosomiasis.[14, 15] Ultrasound-based community surveys can now be used to assess the prevalence of urinary tract pathology and to monitor response to praziquantel treatment. While praziquantel is effective for treating active schistosomiasis infection, the treatment-related reversibility of associated urinary tract structural morbidity is still unclear. Owing to practical and temporal constraints, most cohort studies have focused on a short 12- to 24-month follow-up time after praziquantel treatment.[16-18] The general consensus is that early inflammatory bladder changes such as masses are reversible with timely treatment, particularly if there is no risk of reinfection,[19] whereas chronic changes such as calcification of the bladder, hydroureter, and/or hydronephrosis are much less

likely to resolve.[17, 18, 20-25] A recent systematic review showed that the greatest impact of praziquantel in reducing bladder pathology was seen when follow-up was within 6 months, whereas the chances of finding reversal of pathology decreased as the time to follow up increased.[26] It has also been suggested that urinary tract pathology in adults is less responsive to praziquantel treatment than the pathology seen in children.[18]

The Msambweni region of south-eastern coastal Kenya is endemic for *S. haematobium*. Community based research and control initiatives have been conducted in this area for over 30 years. Annual school-based treatment with PZQ was given between 1984 and 1992, and community-wide treatment has since been given in 2000, 2003, and 2009 as part of ongoing research in the area. Annual treatment of school aged children continues at present. At initiation of the control programme, the prevalence of *S. haematobium* infection was 66% in school age children,[27] and studies in this district have shown a significant reduction in prevalence and intensity of infection after initiation of annual praziquantel treatment.[27, 28]

The aim of the present study was to use portable ultrasound to describe the current prevalence of schistosomiasis-related urinary tract pathology among adults in a treated community that had previously experienced high rates of active urogenital *S. haematobium* infection. We also aimed to compare urinary tract pathology in a cohort of women examined at two time points, 14 years apart, following implementation of community-based control.

MATERIALS AND METHODS

[Figure 1 near here]

Data for the present study were collected between May and July 2014 in the rural villages of Nganja and Milalani, located at 4.5°S and 39.5°E, within the Msambweni region of Kwale County on the coast of Kenya (Figure 1). At last census, in 2013, the two village populations were 836 and 1940, respectively. This study was part of ongoing community-based schistosomiasis research within the district.

Each village was split into 10 areas to ensure participation from households in all sectors of the study villages. Each day, field workers canvassed one of the 10 areas and invited a convenience sample of approximately 30 eligible women to participate in the study. Exclusion criteria were acute febrile illness, inability to give informed consent, and suspected or confirmed pregnancy.[29] Males and children (aged under 18 years) were excluded as the majority of these groups were away from the village during working hours, and therefore a representative sample could not be guaranteed for those sub-groups. Demographic information, including participant name, date of birth, and household number, was gathered by questionnaire to allow for identification of subjects who had participated in previous 2000 era ultrasound surveys.[30]

Parasitological testing

Urine samples were collected between the hours of 10:00h and 14:00h to coincide with peak egg excretion.[31] Egg count was assessed using a standard filtration method as previously described:[32] 10ml of urine was passed through a 10µm polycarbonate filter (Millipore, UK) which was then fixed onto a microscope slide and one drop of iodine was placed on the filter. The slide was examined under light microscopy at 40X magnification.

The intensity of infection was classified according to standard convention,[32] i.e., between 1 and 50 eggs per 10mL was considered a light intensity infection and greater than 50 eggs per 10 mL was considered a heavy infection. Parasitological testing was performed after the ultrasound to eliminate observer bias during interpretation of the images.

Ultrasound assessment

Ultrasound assessments of the urinary tract were performed by a highly experienced study ultrasonographer from the Kenya Medical Research Institute CCR Radiology Unit (EI) and the study doctor (KM) using a portable Siui CTS 7700 PLUS machine and 3.5-5 MHz convex array probe. Quality assurance and final interpretation was provided by study leader EJ. Findings were recorded and scored using WHO standardised criteria for ultrasound of urogenital schistosomiasis [15]. The presence of bladder wall masses, pseudopolyps, irregularities, bladder wall thickening, abnormal bladder shape, ureteric dilatation, and/or hydronephrosis was recorded. Before ultrasound examination, participants were given sufficient fluid to ensure that the bladder was adequately filled. If any ureteric or renal pathology was found, this was re-assessed 30 minutes after urination to eliminate any false positive results caused by overfilling of the bladder.[15]

Longitudinal follow-up

Individual level data from a previous ultrasound survey of the same villages, performed in in 2000, were made available by FMM, PM, and CHK.[30] A participant was considered properly matched if she had the same identifying criteria for two out of three identification categories (name, year of birth, household). In the new (2014) study, a total of 275 women were surveyed. Of these, 102 were tracked and identified as having

participated in the earlier study undertaken in 2000. Of those, 93 of the 102 had had an ultrasound examination in the previous study. Nine were excluded, either due to pregnancy or because they were under the age of inclusion for treatment in 2000 (see flow chart shown in Figure 2).

[Figure 2 near here]

Statistical analysis

Information was collected using data collection sheets and was then entered and collated using Microsoft Excel. The data were then analysed using SPSS software (IBM version 21). Descriptive analysis and 95% confidence intervals (95% CI) were used for comparison of the prevalence of urinary tract abnormalities and of active infection in the 2000 and 2014 data.

RESULTS

Study population demographics

Two hundred seventy-five women were included in the 2014 survey; 108 participants from the village of Nganja and 167 from Milalani. The median age of the women was 40.5 years (range 18 – 84). Table 1 shows the breakdown of egg-patent infection and rates of urinary tract pathology detected in each village.

Prevalence of egg-patent infection and urinary tract pathology in 2014

In 2014, the overall prevalence of active egg-patent schistosomiasis was 6.9%. The infection rates in the two villages were similar (8.3% (9/108) in Nganja vs. 6.0% (10/167) in Milalani). Eighty-nine percent (17/19) of those infected had low intensity egg counts on light microscopy, defined as fewer than 50 eggs per 10mL of urine. Of those

infected, the geometric mean egg count was 6.3 (range 1-368) eggs per 10mL urine. The arithmetic mean egg count was 44 eggs per 10mL urine.

[Table 1 near here]

Schistosomiasis-related urinary tract abnormalities detected by ultrasound were found in 45/275 (16.4%) of women surveyed in 2014 (N=275). Prevalence of ultrasound abnormalities in the two villages was similar, with 19/108 (17.6%) having detectable abnormalities in Nganja and 26/167 (15.6%) in Milalani. Bladder pathology was much more common than pathology of the upper urinary tract. The breakdown of these and other ultrasound abnormalities detected is shown in Table 2. Examples of urinary tract pathology found on ultrasound are shown in Figure 3. Egg-patent infection was found in 9% (4/45) of women with ultrasound abnormalities, compared to 7% (15/229) among women with normal ultrasounds.

[Table 2 near here]

[Figure 3 near here]

Longitudinal cohort: changes of infection and morbidity from 2000 to 2014

Table 3 and Figures 4 and 5 show the comparative egg-patent infection and pathology rates for the 93 women having examination data in both 2000 and 2014. The rate of egg-patent infection within the longitudinal cohort dropped significantly, from 34% (32/93) in 2000 to 9% (8/93) in 2014 (χ^2 = 18.3, p<0.001) but, whilst not statistically significantly different, the prevalence of urinary tract pathology increased from 15% (14/93) to 19% (18/93). Of the 14 who had been affected in 2000, 11 had cleared their abnormalities whereas 3 still had abnormal findings - three had persistent ureteric dilatation, one had persistent unilateral hydronephrosis, and one had persistent bladder

wall thickening and a mass. Overall, the rate of upper urinary tract pathology in the longitudinal cohort remained relatively stable, with 6/93 participants in 2000 and 4/93 participants in 2014 showing either ureteric or renal pathology. However, within this cohort, the presence of bladder wall thickening had increased by 50% (8/93 in 2000 to 12/93 to in 2014, (difference NS)) and, whilst less common, bladder shape abnormality had increased from 1/93 to 3/93, (difference NS).

[Figure 4 near here]

[Figure 5 near here]

DISCUSSION

To the best of our knowledge, this is the first use of ultrasound assessment for longitudinal follow up of schistosomiasis pathology over an extended multi-year time period where intermittent distribution of praziquantel has taken place. As expected following implementation of treatment campaigns, the prevalence of active infection was lower than in previous surveys; in the study villages, it had been observed that egg-patent infection among school age children had fallen from 63.2% in 1984,[28] to 33.2% in 2000-2001.[30] Whilst the 6.9% egg-patent infection rate among adult women in 2014 cannot be directly compared to the previous population-level data, it was much lower than the 23% (34/147) infection rate found among untreated adult women in two neighbouring villages in 1986.[33] The successful schistosomiasis control programmes in the study area have now included ongoing mass drug administration for school aged children, improved education of schistosomiasis symptoms and prevention in the area, periodic mass drug administration for adults, improved sanitation of the villages, and the installation of wells to provide greater access to clean water.[34]

Bladder wall thickening was the most common form of pathology found on ultrasound, which replicates the findings of earlier ultrasound studies of urogenital schistosomiasis pathology in other endemic areas.[35-37] Interestingly, we found more urinary tract pathology than egg-patent infection among adult women in both villages. There are several plausible explanations. Firstly, adults are more likely to have a low egg-excretion intensity infections, in which eggs remain likely trapped within the bladder wall with fewer eggs shed into the urine, a situation that leads to false-negatives as egg exit sites become blocked by fibrosis. In these cases, the active infection is often not detected on urine microscopy of a single urine specimen, as the diagnostic yield is reduced in lower intensity infections.[38]

It has also been shown previously that the excreted egg count in urine does not necessarily correlate with fibrotic pathology among adults, [35, 39, 40] and that the likelihood of pathology can be related to an excessive (unmodulated) immune response rather than to the number of excreted eggs *per se*.[41, 42] This suggests that in our study's population of adult women there is ongoing morbidity despite no detectable active infection. In endemic areas, older age suggests greater exposure to repeated *Schistosoma* infection and therefore an increased cumulative exposure to trapped schistosomal eggs. Thus, adults present with consolidated anatomical structural damage (as sequelae of their experience with chronic infection) that can be less likely to revert after the treatment-related clearance of the parasite.[24] In an area of high transmission in Zanzibar, Lyons and colleagues[43] found more urinary tract pathology than active schistosomiasis infection, whilst in a low transmission area on the same island the prevalence of urinary tract pathology and active infection were the same. This suggests that the proportion of urinary

tract pathology outlasting active infection is more closely related to the aggregate, or cumulative, egg exposure(s) of those specific populations.

The present study included a longitudinal cohort of women having two sequential ultrasound examinations, 14 years apart, in order to estimate risk of long-term schistosomiasis-associated urinary tract pathology in a *S. haematobium*-endemic setting that had received intermittent community-based mass treatments. Whilst in the interval between 2000 and 2014, active, egg-patent infection rates dropped significantly, prevalence of urinary tract pathology was marginally increased within our cohort. This suggests that although bladder pathology may have improved in the short term after praziquantel treatment,[26] recurrent infections suffered by these women may have caused damage within the bladder wall (leading to abnormal shape and thickening) with further progression during successive infections. Upper urinary tract pathology, whilst uncommon, remained present in 50% of those who had been found with upper pathology in 2000. This supports current understanding that ureteric dilatation and hydronephrosis are late stage changes that do not respond to praziquantel treatment.[17, 18, 20-23, 25]

Certain limitations to our study are worthy of discussion. Foremost, as our focus was on adult women, children and adult males were not included, which limits the age- and gender-generalizability of our findings. The process of matching participants to previous data from 2000 limited the lookback cohort size and associated study power. We used a matching process requiring at least two identifying criteria (name, year of birth, or household) to ensure that participants were accurately matched to their 2000 data. Many participants were unsure of their exact date of birth or had changed their names, whilst the villages had expanded greatly in 14 years, making it difficult to track the

movement of some households due to relocation. Because of lack of interval testing, we cannot conclude whether the 2014 pathology seen in this cohort was due to any current, low intensity *S. haematobium* infection (potentially not detected on egg microscopy) or whether it was due to exposure during previous infections. In addition, although of potential interest, the multiplicity of a subject's intervening non-study praziquantel treatment frequency could not be independently confirmed. Assessment for urine for current leukocytes, erythrocytes, or eosinophils was not done, but could have helped to identify ongoing inflammation of the urinary tract at the time of the 2014 survey. In consideration of diagnostics, future studies should involve more sensitive diagnostic assays (augmenting baseline methods) for better differentiation of active infection(s) in order to distinguish between our two hypotheses. Finally, it remains enigmatic whether schistosomiasis-associated urinary tract pathology does or does not correlate with genital tract manifestations. As public health recognition of the importance of female genital schistosomiasis grows,[44] looking ahead, future studies should attempt to integrate urinary and genital morbidity assessments and correlate ultrasound findings with infection markers from both urine and genital samples.

Despite these limitations, our study supports the need for interventions such as mass drug administration, targeted from the age of first exposure to *Schistosoma* infection, to be repeated at regular intervals to reduce cumulative egg exposure.[45] This could prevent the evolution of more advanced chronic disease, which becomes less reversible with treatment.[26] In the 2014-2023 interval since this study was performed, national helminth control programs have continued among school age children, and access to primary health care has improved within the study area. With a greater

303 understanding of the true disease burden of this neglected tropical disease, and by
304 targeting even younger children in mass praziquantel administration to prevent early
305 development of chronic morbidity, we can further strengthen the current efforts to control
306 and eliminate schistosomiasis.

307 **CONCLUSIONS**

308 This is the first study to assess prevalence of schistosomiasis-associated urinary
309 tract pathology following a prolonged 14 year interval. We have found that ultrasound-
310 detected morbidity overshadows egg patent infection among adult women in this area,
311 and therefore the disease burden in this population is greatly underestimated when using
312 egg microscopy surveillance only. The increased availability of portable ultrasound now
313 allows for surveillance of chronic pathology alongside egg microscopy in field studies.
314 Future disease burden estimates should be adjusted accordingly to include risk of chronic
315 morbidity as well as egg-patent infection.

316

317 **Authors' contributions**

318 EJ, KM, AB, JRS, and ALB conceived the study; EJ, KM, AB, FMM, ALB and CHK
319 designed the study protocol; EJ, KM, EI, and AB carried out the clinical assessments; AB,
320 FMM, and PM carried out the laboratory testing, EJ, KM, ALB, and CHK did the analysis
321 and interpretation of the data; KM drafted the manuscript; EJ, ALB, JRS, and CHK
322 critically revised the manuscript for intellectual content; All authors read an approved the
323 final manuscript. EJ, ALB, and CHK are guarantors of the paper.

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Competing Interests

None declared

Ethical approval/ Human subjects

All participants provided individual written informed consent in accord with the guidelines of the Declaration of Helsinki. Ethical approval for this study was granted from Liverpool School of Tropical Medicine, Liverpool, UK (study number 14.014) and Pwani University, Kilifi, Kenya (study reference ERC/MSc/004/2014). All participants had access to translated study information and gave written informed consent before their inclusion. Any information presented here has been anonymized as much as possible. Those participants found to have active schistosomiasis infection during the survey were treated with praziquantel at a dose of 40mg/kg after the study, as recommended by WHO. In the

2000 era surveys, the research protocol was approved by the Ethical Review Board of the Kenya Medical Research Institute (KEMRI/RES/7/3/1) and the Institutional Review Board for Human Investigation of University Hospitals of Cleveland (protocol 03-88-34). All subjects found to be infected with *S. haematobium* were treated with standard doses of praziquantel (PZQ) (40 mg/kg) immediately after the initial morbidity survey.

Data Availability/Supplementary Data

Anonymized individual-level outcomes data are provided in an accompanying Supplementary Table (Supplementary Data file for Joekes et al.xlsx)

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FIGURE LEGENDS

Figure 1. Map showing the location of the Msambweni region of Coastal Kenya. (from Bustinduy, et al., PLOS Neglected Tropical Diseases, 2011, 5(7): e1213. doi:10.1371/journal.pntd.0001213; used with permission under Creative Commons Attribution License)

Figure 2 – Flow diagram of participants matched to both 2000 and 2014 data for cohort analysis

Figure 3 – Ultrasound images showing urinary tract pathology detected in 2014. (A), transverse image showing an abnormally shaped/rounded bladder; (B), transverse image of bladder wall thickening; (C), transverse image showing ureteric dilatation; (D), a sagittal image of the right kidney showing severe hydronephrosis.

Figure 4 – Longitudinal change in prevalence of egg-patent infection and pathology on ultrasound between 2000 and 2014 (N=93)

Figure 5 – Prevalence of egg-patent infection and urinary tract pathology in a cohort of 93 studied women, comparing results in 2000 to those in 2014

Figure 1

Click here to access/download;Figure;Joekes et al Figure 1.tif

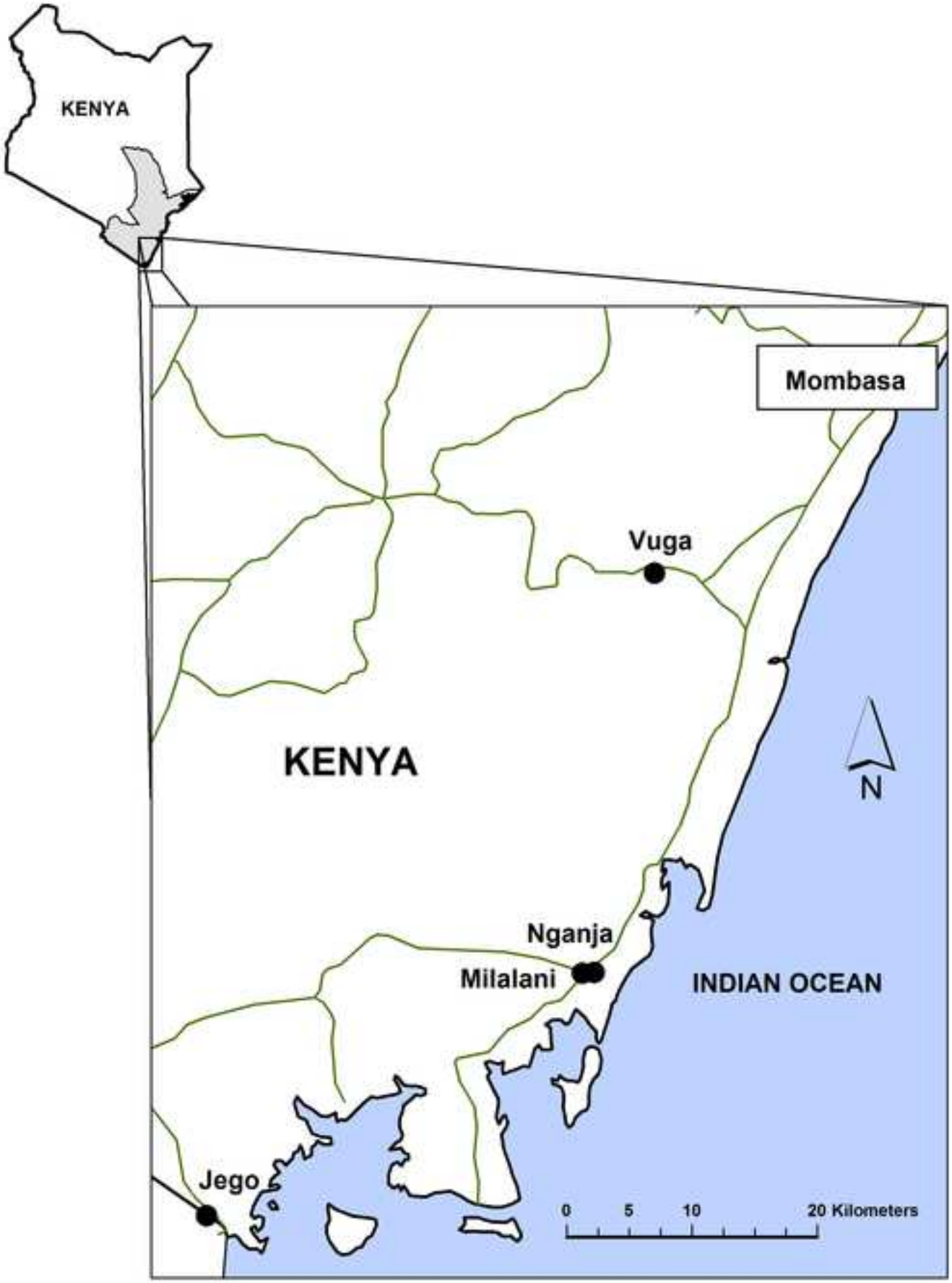


Figure 2

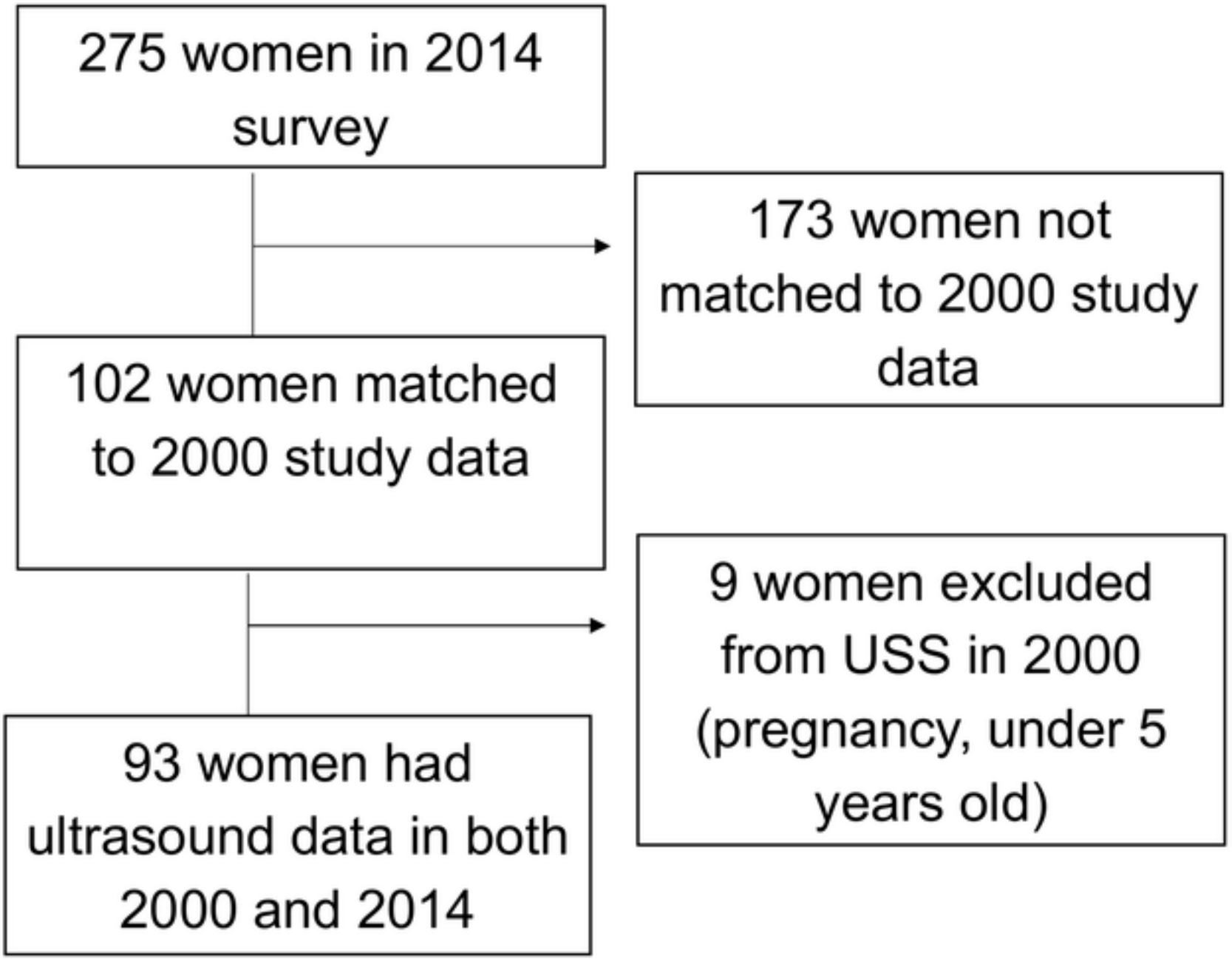


Figure 3

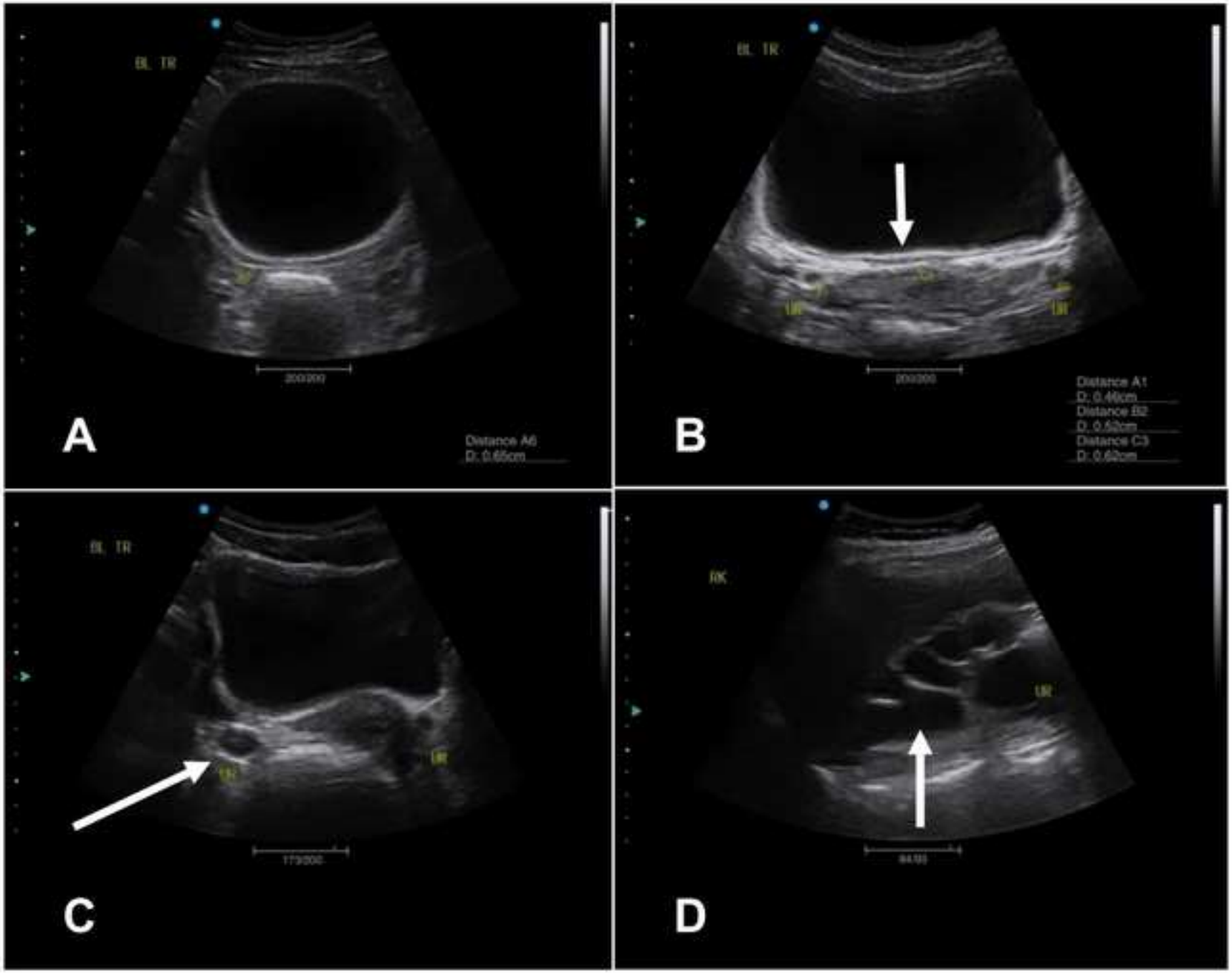
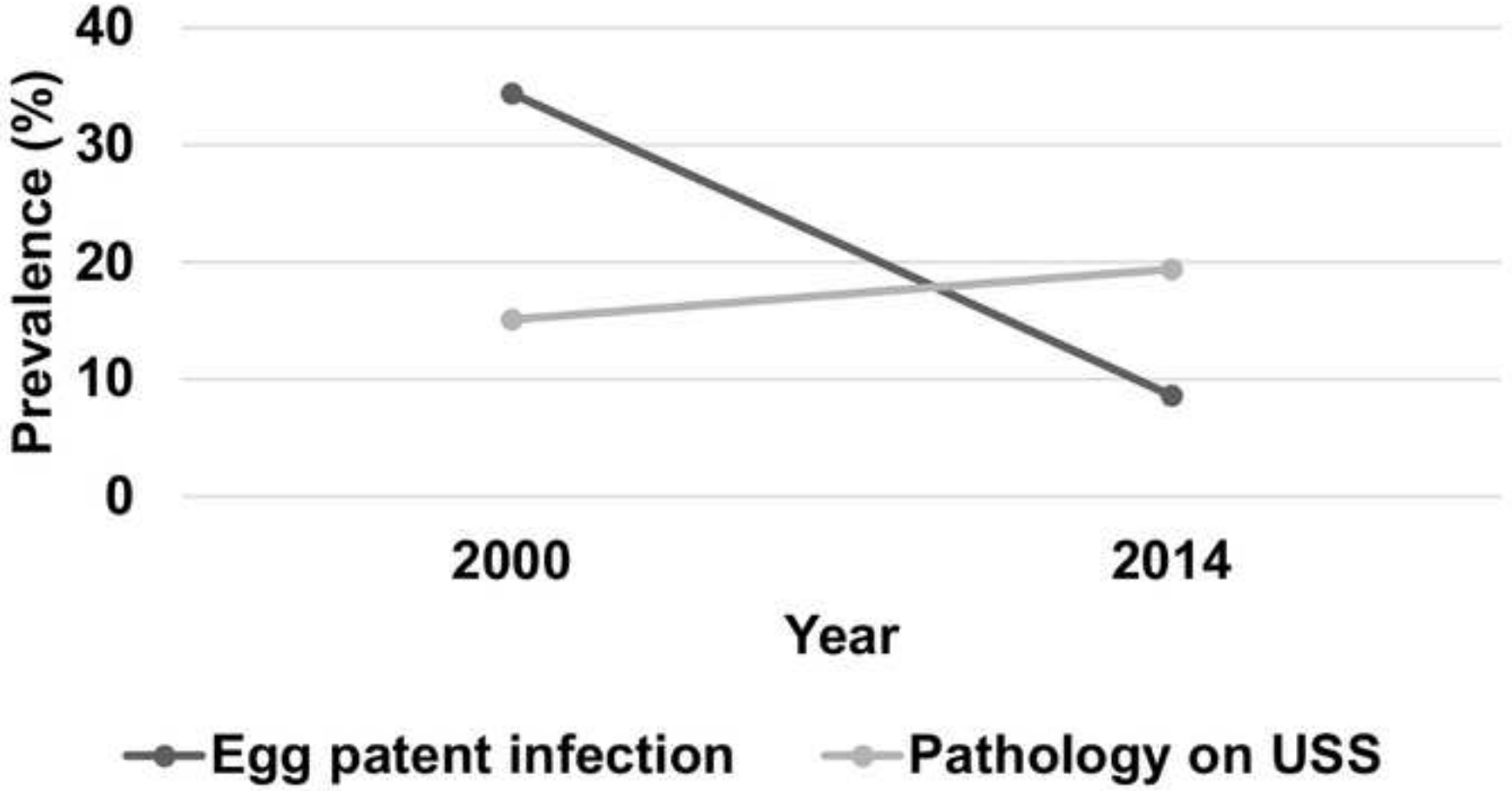


Figure 4



Figure

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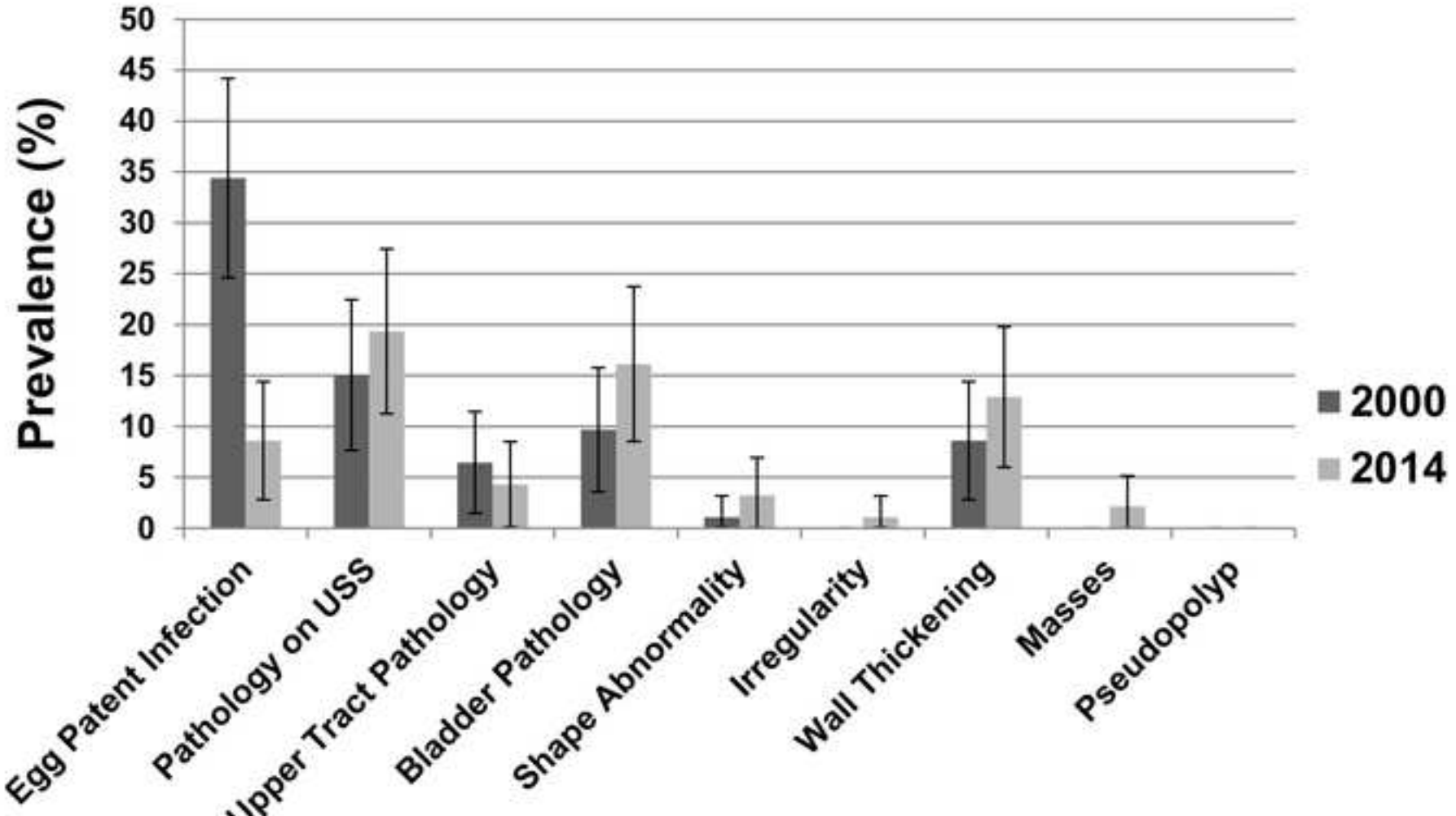

Table 1 – Demographic data, prevalence of egg-patent infection and urinary pathology among surveyed women in 2014, N=275

	Nganja	Milalani
Participants	108	167
Median age in years (IQR)	41.0 (33.5-52.5)	39.5 (29.5-53.5)
Egg-patent infection (%)	9 (8.3%)	10 (6.0%)
Urinary tract pathology (%)	19 (17.6%)	26 (15.6%)

Table 2 – Number (n) and prevalence (%) of community-level egg-patent infection and ultrasound-detected urinary tract pathologies among 275 women tested in 2014

	n	% of total (N= 275)	95% CI
***S. haematobium* prevalence by parasitology**	19	6.9%	3.9-9.9%
Intensity (per 10ml urine) **Light (1-50)** **Heavy (≥50)**	17 2	6.2% 0.7%	3.9-9.7% 0.0-1.7%
Pathology on US	45	16.4%	12.0-20.8%
Bladder Pathology	39	14.2%	10.0-18.3%
Abnormal shape	7	2.5%	0.7-4.4%
Irregularity	2	0.7%	0.0-1.7%
Thickening	33	12.0%	8.1-15.9%
Mass	2	0.7%	0.0-1.7%
Pseudopolyp	0	0.0%	
Upper tract pathology	8	2.9%	0.9-4.9%
Unilateral ureteric dilatation	2	0.7%	0.0-1.7%
Bilateral ureteric dilatation	5	1.8%	0.2-3.4%
Unilateral hydronephrosis	2	0.7%	0.0-1.7%
Bilateral hydronephrosis	2	0.7%	0.0-1.7%

Table 3 –Individual level data of egg-patent infection and urinary tract pathology among the cohort of 93 women examined in 2000 and again in follow up in 2014

	2000		2014	
	n	**% of total (N=93) (95% CI)**	**n**	**% of total (N=93) (95% CI)**
Egg-patent Infection	32	34% (25-44)	8	9% (3-14)
Any Urinary Tract Pathology	14	15% (8-22)	18	19% (11-28)
Upper Tract Pathology	6	6% (1-11)	4	4% (0.1-8)
Any Bladder Abnormality	9	10% (4-16)	15	16% (8-24)
Abnormal Shape	1	1% (0-3)	3	3% (0-7)
Bladder Irregularity	0	-	1	1% (0-3)
Wall Thickening	8	9% (3-14)	12	13% (6-20)
Masses	0	-	2	2% (0-5)
Pseudopolyps	0	-	0	-