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Mussel RL, De Sa Silva E, Costa AM, Mandarim-De-Lacerda CA (2003). Mast cells in tissue response to dentistry materials: an adhesive resin, a calcium hydroxide and a glass ionomer cement. J. Cell. Mol. Med. 7:171-178.

Booth M, Bundy DA, Albonico P, Chwaya M, Alawi K (1998). Associations among multiple geohelminth infections in school children from Pemba Island. Parasitol. 116: 85-93.0.

Fransiscus RG, Long JC (1991). Variation in human nasal height and breath, Am. J. Phys. Anthropol. 85(4):419-427.

Stanislawski L, Lefeuvre M, Bourd K, Soheili-Majd E, Goldberg M, Perianin A (2003). TEGDMA-induced toxicity in human fibroblasts is associated with early and drastic glutathione depletion with subsequent production of oxygen reactive species. J. Biomed. Res. 66:476-82.

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Full Length Research Paper

Parental perceptions and home management of pyrexia in children in a malaria endemic area

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Fever is one of the most common symptoms of disease in children, accompanies a range of illnesses and is often treated at home before medical attention is sought. An investigation of fever management among parents of children under five was carried out to evaluate parental perception. Parents of 1143 children were randomly selected and interviewed to answer a questionnaire about fever. Majority of parents (63%) perceived fever to be hotness of the body and had no idea of the normal body temperature and so did not use a thermometer. 621 parents representing 54% irrespective of their educational qualification and age suspected malaria as the most likely cause of fever which made them act within 24 h by administering antimalarial drugs at home without medical diagnosis. Parents felt that an untreated fever could result in convulsion (16%) and even death (14%) which informed some harmful practices. The educational level of parents was statistically insignificant ($p>0.05$) and had no bearing on the knowledge of fever while the age of parents had a strong correlation with their perception and fever management. Based on the outcome of this study, there is a need for appropriate education to prevent the abuse of antimalarial drugs and also to stop some crude and harmful practice employed to arrest a convulsive child.

Key words: Fever, parental, perception, management, children.

INTRODUCTION

Fever is common in childhood and parents have been shown to have unrealistic fears of the harmful effects of fever to their children. Therefore they tend to overestimate its dangers, and make inappropriate telephone calls and unnecessary clinic visits, leading to excessive utilization of healthcare services (Schmitt,1980; Adam and Stankov, 1994). It should however be considered that, since the underlying cause of fever contributes to morbidity and mortality the fears and actions based on these fears of parents may be viewed as justified. An elevation of temperature is perceived as fever by parents and it is one of the most encountered symptoms given by parents to clinicians in pediatrics emergency rooms and clinics as signal of illness of the child (Crocetti et al., 2001).

Fever is however a common symptom of a wide spectrum

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of illnesses and is characterized by an elevation of body temperature above the normal range of 36.5 to 37.5°C (97.7 to 99.5°F) due to an increase in the temperature regulatory set-point. This increase in set-point triggers increased muscle tone and chills. A fever can be caused by many different viral or bacterial conditions ranging from benign to potentially serious. However, fever could also be a defense mechanism as the body's immune response can be strengthened at higher temperatures (Krauss et al., 1991).

As mentioned earlier, there is an unrealistic fear of fever by parents and care givers and this fear is referred to as 'fever phobia". This fear is induced by loss of personal control as the parent is overwhelmed by the perceived threat of something bad happening to the child. Schmitt was the first to use this terminology laying emphasis on the unrealistic nature of such fears. The author emphasizes that this unrealistic fear often leads to dangerous actions taken by parents to arrest the situation (Schmitt, 1980).

Fever phobia is still a common phenomenon (Krauss et al., 1991) and may result in parents taking potentially harmful actions, such as use of herbal concoctions, scarification, and excessive use of antipyretics, amongst others because the most dreaded consequence of fever in children is febrile convulsion, which occurs in approximately 3% of all children with high fever by their fifth birthday (Ajayi and Falade, 2006). Some of the harmful actions by parents could even lead to the death of the child and will not help in reducing the under-five mortality rate in Nigeria which is 13% (WHO, 2015). Nigeria already losses about 2,300 under-five year old making the country one of the largest contributor to the under-five mortality rate in the world (NPS, 2008). The Millennium development goal in 2014 was to reduce by two thirds, between 1990 and 2015, the under-five mortality rate. Educational intervention such as health literacy campaign, health education during antenatal/ clinic visit will help improve parental understanding and management of fever and reduce inappropriate physician contacts and medication errors

The purpose of the study was to determine the status of knowledge and attitude of parents about fever in Yenagoa, Southern Nigeria. This result of the study will provide statistics from this part of Nigeria where no data is available and help the health ministry to educate parents about fever.

MATERIALS AND METHODS

The study took place in Yenagoa which is the headquarters of Bayelsa State located in the Niger delta area of Nigeria. Bayelsa state is a tropical rain forest with more than three quarters covered with water and lies entirely below sea level with a maze of creeks and mangrove forest. The sample size for this survey was 1143 patients. Sample size was determined using the formular $n= t^2 \times p (1-p)/m^2$ as described by Magnani (1997). Parents of children within the age range of 0 of 5 years in Yenagoa were invited to participate in the study. Each eligible male or female parent was interviewed by a research assistant, using a standard questionnaire designed to obtain background socio-demographic information and current knowledge of fever. Parents were given no assistance with answering the questions and none refused to be interviewed. In an attempt to obtain unbiased data that truly reflected parents' perceptions about fever, the questionnaire relied principally upon open-ended questions and no suggestions of the "right" answer. Demographic data obtained included age of both parents, level of education attained and current occupation of parents. The questionnaire items were designed to ascertain parents' knowledge, attitudes and fears concerning fever in their child. The questions asked were as follows: How do you know if your child has a fever? what is the normal body temperature; what is the temperature reading that constitutes a fever in a child?; what is the greatest harm that high fever can cause to a child?; what is your method of fever detection, what is your presumptive diagnosis? What action do you take when your child has a fever. Other items used to determine knowledge and perception explored the spheres of: causes of fever and management of fever. The questions were framed in a way as to enable the average lay person to understand and respond, yet an attempt was also made to obtain definitive data.

Statistical analysis

Statistical analysis was performed with the GraphpadPrism version 4® (Graphpad software, San Diego, CA). Differences between groups were determined by the one way analysis of variance (ANOVA) or paired t- test with the level of significance set at $p < 0.05$.

RESULTS

A total of 1143 parents of children under 5 years were interviewed and a description of the socio-demographic characteristics of the study parents is presented in Table 1. The majority of parents interviewed were living in Yenagoa while others came from the adjoining towns. The mean ages of the children were 2 years and 5 months with a male to female ratio of 1:1. Parents recruited for the survey had their mean age range as 28 years and 8 months with a father to mother ratio of 1:3. Parental knowledge and perception of fever is shown in Table 2.

Tactile method of touching the forehead and body parts of the child was the most utilized method for detecting a fever by the parents. This method was employed by 1008 (88%) of the parents while a small fragment 135 (12%) makes use of a thermometer. Parts of the body touched to detect fever by parents were the forehead 180 (15%), neck 90 (8%), stomach and back 270 (24%), combination of all 603 (53%). Majority of parents interviewed (47%) had no idea of the normal range of the body temperature, some parents gave values higher (7%) while others (20%) gave lower values and 24% knew the correct normal temperature range. Recognition of fever by 720 parents (63%) was an increase in body temperature, 162 parents (14%) felt a weak child was a sign of fever, 90 (7.9%) knew their

Table 1. Socio-demographic characteristics of 1143 study parents.

Characteristic	Number	%
Parent		
Father	261	**23**
Mother	882	77
Residence		
Yenagoa	1000	87.5
Outside Yenagoa	143	12.5
Age of parent (range 15 to 60 mean 29)		
> 30	648	57
40-49	315	27
>50	180	16
Parent's education		
Illiterate	225	20
Primary	306	27
High school/secondary school	360	31
University graduate and above	252	22
Parent's occupation		
Skilled	468	41
Unskilled	378	33
Student	45	4
Unemployed	252	22

child has a fever with a convulsive fit. Blisters at the side of the child's mouth was a sign of fever for 90 parents (7.9%) while another 81 (7%) had varying ways of recognizing a fever such as a lack of appetite, restlessness and rashes on the body.

Fever phobia was expressed in different ways, out of the 1143 participating parents, 54.3% cause of fever phobia was malaria and 20 parents (15.7%) perceived a fever could lead to convulsion with majority in the graduate category. The child's death was the perception of 162 (14.2%) parents while 90 parents representing 7.9% perception of a fever was an infection. 90 parents out of the 1143 parents had no idea what a fever could lead to. Presumptive diagnosis by parents were malaria (42%), teething (30%), diarrhea (24%) while 48 parents thought the fever was as a result of an infection representing 4%. Parents were asked what action they took when they noticed their children had a fever, 605 parents acted within 24 h while 477 acted after 24 h and 63 interviewed their child only without taking any other action.

Action taken by the parents ranged from visiting a chemist (28%) and herbal treatment (16%) to visiting a government hospital (17%). Other actions taken by parents were laboratory investigations (8%) and home treatment or medication (31%). Parents who did self medication at home were asked what type of medication was used. Out of the 1143 parents recruited into the study, 396 representing 35% gave their children an antimalarial, 17% gave antibiotics, 16% used local herbs, and 25% used both antimalarial and antibiotics while 8% administered an antipyretic only.

DISCUSSION

This study showed that there is considerable anxiety and misinformation about fever in the population surveyed, and that this anxiety is related to aggressive early treatment of fever. Previous studies in Nigeria (Ajayi and Falade 2006; Fawole and Onadeko 2001; Salako et al., 2001), Africa (Deming et al.,1989; Lubanga et al., 1997) and other parts of the world reveal the same anxiety which Schmitt labeled "fever phobia" as a worldwide phenomenon (Schmitt 1990).

Overall findings of this study suggest that parents had minimal knowledge of fever and this knowledge also informed early and aggressive treatments. Our finding collaborates with the report in Enugu (Tagbo et al., 2010) and Illorin (Abdulkadir and Johnson, 2013) respectively. Tactile method of fever assessment is a common practice in most homes and communities and used to a large extent as reported by other findings (Tagbo et al., 2010; Oshikoya et al., 2008; Abdulkadir

Table 2. Parental knowledge and perception of fever.

Characteristic	Number	%
Recognition of fever		
Increase in body temperature	720	63
Weakness	162	14
Convulsive fit	90	7.9
Blisters	90	7.9
Others	81	7.0
Method of fever detection		
Thermometer	135	12
Tactile	1008	88
Knowledge of body temperature		
Above normal	99	7
Below normal	234	20
Normal	270	24
No idea	540	47
Parental fever phobia		
Malaria	621	54
Convulsion	180	16
Death	162	14
Infection	90	8
Others	90	8
Parent's presumptive diagnosis		
Malaria	483	42
Teething	306	30
Diarrhea	270	24
Infection	48	4
Intervention by parents		
Acted within 24 hours	603	53
Acted after 24 hours	477	41
Interviewed child only	63	6
Action taken by parent		
Visiting a government hospital	189	17
Visiting a chemist	324	28
Herbal treatment	180	16
Laboratory investigations	90	8
Home treatment	360	31
Drugs used at home		
Antimalarial	396	35
Antibiotics	189	17
Antipyretics	90	8
Antibiotics and antimalarial	288	25
Local herbs	180	15

and Johnson, 2013), this also conforms to this study where 88% of parents used the dorsum of the hand in detecting a fever. Despite the fact that the specificity of this method is not 100% accurate and limited to that of a screening tool (Deming, 1999), it was still the choice of detecting a fever by majority of parents. Generally observed from this study, is the common perception by parents that the head, abdomen and back were the most important parts of the body from which fever is detected. Fore head tactile assessment findings from this study is also similar to the findings of singh et al. (2003) who reported that adults felt the fore head to identify fever.

Parents showed little understanding of the normal range of body temperature and individual diurnal variation, as well as demonstrating inadequate knowledge of what actually constitutes a fever. This report is similar to studies in some other urban cities in Nigeria (Ajayi and Falade 2006; Fawole et al., 2001; Salako et al., 2001; Tagbo et al., 2010) and in other parts of Africa (Deming et al.,1989; Lubanga et al., 1997) but contrary to a study in Lagos (Oshikoya, 2008) where mothers were quite knowledgeable of fever. The researchers were also surprised that parents of high socio-economic and educational status were not different in terms of knowledge of fever from parents of lower socioeconomic/ educational background and limited previous experience. It seems that healthcare providers have not done enough in educating parents in this basic information.

The definition of normal body temperature is complex. DuBois in 1948 found the normal ranges of body temperature for children to be from a low of 36.2°C to a high of 38.0°C when measured rectally, and from 36.0°C to 37.4°C when taken orally. The maximum body temperatures for children occur between 5 and 7 p.m., and the minimum temperatures occur between the hours of 2 and 6 a.m. Hence, it is not unusual for an active normal child's temperature to be as high as 38.0°C rectally in the late afternoon. A rise in temperature above 38.0°C may also be caused by physical exercise, warm clothing, hot or humid weather, or warm food/drinks and such external factors should be put into consideration before measuring the temperature. Fever is defined as a temperature above the normal range. A rectal temperature of 38.0°C or more, an oral temperature of 37.5°C or more, and an axillary temperature of 37.2°C or more, are all considered fever (Mackowiak, 1991). .

About 24% of the responding parents could identify what constitutes the normal body temperature, and another 47% did not know what value is referred to as a normal body temperature. This is of great concern as most parents did not know that temperature constitutes a fever and this ignorance could be the reason why there is great fear and anxiety and such aggressive methods in treating a feverish child. Highest presumptive diagnosis by parents was malaria which conforms to other reports by other Nigerian researchers (Ajayi and Falade 2006; Fawole et al., 2001; Salako et al., 2001; Tagbo et al., 2010) and other African countries (Deming et al., 1989; Lubanga et al., 1997). This diagnosis by parents may be due to the endemic nature of malaria in Africa and also the fact that it is the major ailment affecting

children below five years in the continent. The large proportion of parents presumptive diagnosis of malaria is a cause of concern because over diagnosis of malaria can cause other life threatening conditions that require urgent medical attention, such as septicaemia, bronchopneumonia, tonsillitis and meningitis to be missed out by the parents and further delay their treatments. There is a need to educate parents especially mothers on how to recognize malaria with complications and other life threatening conditions that may mimic malaria so as to present their child early to the hospital. The causes of parental phobia of untreated fever in this study ranged from malaria, convulsion, infection and even death. The findings suggest that anxiety, which Schmitt labeled "fever phobia", is a widespread phenomenon as it conforms to other studies in parts of Nigeria (Ajayi and Falade 2006; Fawole et al., 2001; Salako et al., 2001; Tagbo et al., 2010) and in other parts of Africa (Deming et al.,1989; Lubanga et al., 1997) and the world (Stephenson, 1988; Chiapinni et al., 2012) at large. The high level of parental anxiety could be explained in several ways. The parent may have overestimated the seriousness of the conse-quences of fever or if unaware of the consequences, experienced fear of the unknown. The anxiety level could be greater if the parent has little experience in dealing with fever.

Management of fever at home by parents and care givers seems to be a common practice in most homes where it is referred to as home treatment or home doctoring. Home treatment in the context of this study, refers to the use of previously prescribed drugs, over the counter drugs, left-overs of previously used/prescribed drugs, non-prescribed drugs for a particular ailment or re-filling prescribed drugs with an old prescription without consulting with a doctor. The presumptive diagnosis of the doctors who attended to the sick children with fever might have accounted for the knowledge of what type of drug to use. The implication of this is not only the positive influence it has on the mothers to keep such drugs at home but the promotion of home doctoring which encourages misuse and overuse of such drugs. 31% of parents in this study managed their child's fever at home without seeking for professional help and only did so when there was no change in the condition. Management of fever at home by parents seems to be a practice in most parts of Nigeria as documented by previous researchers (Ibeh et al., 2005; Akogun and John, 2005) and also from the result of this study and this might be due to the poverty level. There is a need for further research on why parents engage in home management of fever instead of seeking professional help.

Antimalarials such as chloroquine and sulphadoxime/pyrimethamine) were the drugs used in home treatment of fever in the findings from previous studies (Fawole et al., 2001; Salako et al., 2001) but in this study, parents used more of Artemisinin combined therapy (ACT) and this could be as a result of the introduction of ACTs as the first line drug for treating malaria and its availability in the open market. Presumptive treatment of all childhood fevers as malaria by most parents' results in malaria over diagnosis which means other causes of febrile illness will be missed until a much later time when the child's condition does not improve. Such trend is a cause for alarm because of the risk of resistant strains of the plasmodium parasite to ACTs emerging.

Home use of antibiotics as observed in this study is of great concern. The 17% rate utilized in this study is similar to the 13.5% antibiotics utilization rate documented in Lagos (Oshikoya et al., 2007) lower than 31.3% previously reported in Eastern Nigeria (Ibeh et al., 2005) and much lower than 62.0% reported in Iraq. It was noted that some parents in this study combined both antibiotics and antimalarial. The implication of this is that the children are at risk of developing adverse reactions since antibiotics constitute the leading cause of moderate to severe adverse drug reactions in children (Jaryawadene, 1993).

Also, the potential for antibiotic resistance and treatment failure could be high in such children. These drugs are easily obtained over the counter from pharmacies, chemists and even medicines shop without a prescription card. The accessibility to obtaining over the counter drugs could be the reason why 28% of parents in this study visited the chemist instead of going to the hospital and seeking professional help. Only 8% of parents did a laboratory investigation before giving drugs to their ward. This shows that there is a low awareness of the importance of laboratory investigations in proper health care delivery and there is a need to educate parents on the relevance of such investigations in proper diagnosis. Use of herbal medicine as observed in this study is not peculiar only to this study where 16% of parents resorted to herbal treatment of a fever, it is a common practice in Nigeria and has been documented by different researches (Ajaiyeobaet al., 2003; Ishola et al., 2014).

This study was done in an urban setting; the situation may be very different in a rural setting where people are at disadvantages of good health care facilities, quality education and poverty. A similar study in the rural setting is suggested so as to achieve generalized application of the observed interventions of fever home managements.

Conclusion

Parents in the study population had a poor knowledge of fever, normal body temperature and method of detection. This knowledge gap is likely to impact negatively on decisions regarding the home management of fever, presentation at a health facility, and the eventual outcome of febrile illnesses. Health education interventions such as health literacy campaigns and fever therapy talks during clinic visit will improve parental understanding and

management of fever

Conflict of Interest

The authors report no conflicts of interest.

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Full Length Research Paper

Comparative evaluation of pattern of abnormalities in hysterosalpingography, diagnostic laparoscopy and hysteroscopy among women with infertility in Zaria, Nigeria

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Laparoscopy and hysteroscopy procedures commenced recently in our center and no study has been done on them yet. Also, there is paucity of information in our environment on comparison of laparoscopy/hysteroscopy findings with hysterosalpingography (HSG) amongst infertile women. The purpose of this study was to evaluate pattern of the abnormalities detected on HSG in infertile women and to compare them with laparoscopy and hysteroscopy findings. A prospective study of 220 consecutive patients who had HSG between December, 2011 and May, 2013, at Department of Radiology, Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Nigeria was conducted. Clinical notes and radiological findings were analyzed for demographic data, uterine status, tubal and pelvic abnormalities. Findings were correlated with those of laparoscopy and hysteroscopy. Data was analyzed using EPI Info version 3.3.2 for windows. Of the 72 women with tubal occlusion on HSG, 46 (63.89%) women had laparoscopy with dye test. HSG demonstrated unilateral tubal occlusion in 35 (76.09%) women and bilateral tubal occlusion in 11 (23.91%) women. The laparoscopy with dye test also demonstrated unilateral tubal occlusion in 34 (73.91%) women and bilateral tubal occlusion in 10 (21.74) women. The difference in the findings of both tests on tubal patency was not statistically significant (p>0.05). All the 26 women with uterine adhesion on HSG had diagnostic hysteroscopy which confirmed all the cases. There was no difference in the findings of both tests (p>0.05). Both HSG and diagnostic laparoscopy are effective in evaluating tubal patency with no significant difference in accuracy. Also both HSG and hysteroscopy are effective in evaluating intrauterine adhesions with no difference in accuracy.

Key words: Abnormalities, hysterosalpingography, laparoscopy/hysteroscopy, infertility.

INTRODUCTION

Infertility is the failure to conceive (regardless of cause) after one year of unprotected regular sexual intersexual

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(Biotherapeutic Index, 2012). Infertility affects approximately 10 to 15% of reproductive-aged couples (Boudhraa et al., 2009). Its overall prevalence has been stable during the past 50 years; however, a shift in etiology and patient age has occurred (Boudhraa et al., 2009). As a woman's age increases, the incidence of infertility also increases (Biotherapeutic Index, 2012).

Infertility is caused by male and/or female factors. Male and female factors each account for approximately 35% of cases (Ugwu et al., 2012). Often, there is more than one factor, with male and female factors combined causing 20% of infertility (Adegbola et al., 2013). In the remaining 10% of cases, the etiology is unknown (Biotherapeutic Index, 2012). A study conducted in Nnewi, Nigeria revealed a high prevalence of male infertility of whicholigozoospermia and asthenozoospermia which were the most common aetiological factors (Ikechebelu et al., 2003). Female factor infertility can be divided into several categories: cervical or uterine, ovarian, tubal and other (Ugwu et al., 2012). Abnormalities or damage to the fallopian tube interferes with fertility and is responsible for abnormal implantation such as ectopic pregnancy (Adegbola et al., 2013). Obstruction of the distal end of the fallopian tubes may result in hydrosalpinx and pyosalpinx (Boudhraa et al., 2009). Other tubal factors associated with infertility are either congenital or acquired.

Congenital absence of the fallopian tubes can be due to spontaneous torsionin utero followed by necrosis and reabsorption. Elective tubal ligation andsalpingectomy are acquired causes. Tubal factors are responsible for 25 to 30% of infertility cases, with salpingitis being the most common cause, representing more than half of the cases (Chandra et al., 2005). Salpingitis partly contributes to the increased number of infertility cases as the occurrence has increased over the past 2 decades (Honore et al., 1999). Estimates show that after one episode of pelvic inflammatory disease (PID), an 11% risk of tubal infertility is present. This risk increases to 23% after 2 episodes of PID and as high as 54% after 3 episodes (Honore et al., 1999). The uterus contributes about 10% of causes of female infertility. Intra uterine adhesion (Asherman's syndrome) may complicate curettage following pregnancy related disorders. The more common types of fibroid (leiomyoma) that adversely affect reproduction are sub mucous and intra cavitary types. Endometral polyps, if large enough can affect reproduction (Arati, 2004).

Congenital uterine anomalies are seen in about 2 to 3% of all women and approximately 25% of these will have associated infertility. The most common congenital defect associated with infertility is the septate uterus (Kamini, 2004). Other uterine factors causing infertility include adenomyosis and endometritis due to tuberculosis (Preutthipan and Linasmita, 2003). With the recent advances in reproductive medicine, hysterosalpingography has become a relatively quick and non-invasive examination aim to evaluate fallopian tubes and uterine cavity (Ubede et al., 2001). Congenital uterine malformations, technical artefacts and pathological findings are depicted. Pathological findings that can be detected on hysterosalpingography include salpingitis isthmica nodosa, tubal blockage, peritubal adhesion, submucosal leiomyoma, endometrial polyp, endometrial carcinoma, synechiae and adenomyosis (Eng et al., 2007).

During the last 35 years, gynecologic laparoscopy has evolved from a limited surgical procedure used only for diagnosis and tubal ligations to a major surgical tool used to treat a multitude of gynaecologic indications (Ikechebelu et al., 2010). Today, laparoscopy is one of the most common surgical procedures performed by gynaecologists. For many procedures, such as removal of an ectopic pregnancy, treatment of endometriosis, or ovarian cystectomy, laparoscopy has become the treatment of choice (Hurd et al, 2007). In laparoscopy and dye test, the dye test will demonstrate if the fallopian tubes are blocked. The laparoscopy will help identify endometriosis, pelvic infection, adhesions, ovarian cysts or fibroids. Some minor treatments can be performed at the same time (Hawe, 2008). A study done in Osaka Japan demonstrated that diagnostic laparoscopy was beneficial for patients with unexplained infertility and normal HSG findings, as diagnostic laparoscopy was able to help detect the cause(s) of infertility in the pelvic cavity and helped to design a suitable management plan, which could lead to postoperative pregnancy. It was therefore suggested that patients with unexplained infertility and normal HSG findings should undergo diagnostic laparoscopy prior to the assisted reproductive therapy (Tsuji et al., 2009).

Many studies have been performed on comparing HSG and hysteroscopy which is generally indicated for a thorough study of the endometrial cavity (Ganglione et al., 1996; Pellicer, 1988). Whereas, HSG is a good screening procedure for uterine abnormalities, hysteroscopy is used for confirmation and treatment of either abnormalities found on HSG or those cases with normal HSG findings that had no improvement in fertility for at least 6 months (Ganglione et al., 1996). In a comparative study between HSG and hysteroscopy performed on 336 patients the most commonly misdiagnosed conditions are cervical stenosis as severe intrauterine adhesions, endometrial polyps as submucous myomas, and submucous myomas as endometrial plyps (Preutthipan and Linasmita, 2003). The purpose of this study was to evaluate pattern of the abnormalities detected on HSG in infertile women and to compare these findings with laparoscopy and hysteroscopy findings.

MATERIALS AND METHODS

This prospective study was carried out at the Ahmadu Bello University Teaching Hospital (ABUTH), which is a tertiary health institution located in Zaria, Kaduna State, Nigeria. The city has a

Table 1. Age group and type of infertility.

Age group (Years)	Type of infertility		Total (%)
	Primary (%)	Secondary (%)	
18-28	76 (46.4)	92 (54.8)	168 (76.4)
29-40	11 (21.2)	41 (78.8)	52 (23.6)
Total	87 (39.5)	133 (60.5)	220 (100)

Table 2. Uterine and cervical canal findings at HSG.

Characteristic	Uterine findings		Cervical canal findings	
	Frequency	%	Frequency	%
Normal	167	75.9	210	95.5
Adhesion	26	11.8	8	3.6
Fibroid	21	9.5	-	-
Bicornuate UT	4	1.8	-	-
Unicornuate UT	1	0.5	-	-
Septate UT	1	0.5	-	-
Dilatation	-	-	2	0.9
Total	220	100	220	100

UT = Uterus.

population of 975, 153 (National Population Commission, 2006). This prospective study was carried out between 1 December, 2011 and 31 May, 2013 on 220 consecutive patients referred from infertility clinics of the Ahmadu Bello University Teaching Hospital for hysterosalpingography. The subjects were married women with various years of infertility. The exclusion criteria were: ongoing or recent pelvic infection, late menses without confirmation of absence of pregnancy, recent history of intra uterine instrumentation and technical impairment in any of the examinations. The study was approved by the Ethics Committee of our Hospital and all patients gave informed consent. Demographic data such as age, parity, and duration of infertility were extracted from specially designed data collection form. All HSGs were performed by the same consultant Radiologist using the techniques by David and Jamil, (1999). After HSG, those with abnormalities were counseled for laparoscopy and hysteroscopy evaluations. Those that gave their informed consent had diagnostic laparoscopy and hysteroscopy. A specialist Gynecologist performed the laparoscopy and hysteroscopy using the laproscopy and dye test (Hutchon, 2006) and technique by Preutthipan and Linasmita (2003), respectively. The cost of laparoscopy with dye test was three times that of HSG. The information was extracted and subsequently analyzed using EPI INFO Version 3.3.2 for windows. The results were displayed in frequency tables and percentage. Test of significance was done using 95% confidence intervals.

RESULTS

Two hundred and twenty (220) patients with infertility were interviewed and investigated. The age ranged from 18 to 40 years, and shows a normal age distribution curve, with mean age of 27.37±4.50 (Figure 1). The duration of infertility ranges from 1 to 8 years with a mean duration of 4.48±1.24years as shown in Table 1. Table 1 also shows that women with secondary infertility were 133 (60.5%) while primary infertility was 87 (39.5%). The first aged group of 18 to 28 years had a high proportion of primary infertile participants (46.4%) while high proportion of secondary infertile patients, 78.8% were in age group 29 to 40 years. However, there was more secondary infertility in both age groups.

There were 72 (32.7%) patients who had normal HSG, while 148 (67.3%) patients had abnormal HSG. In Table 4, patients aged 29 to 40 years had more abnormal HSG findings (69.7%) than those aged 18 to 30 years (66.7%). The difference was not statistically significant (p-value=0.861). However, patients with secondary infertility had slightly more abnormal HSG findings (72.2%) than those with primary infertility (59.8%). This difference was not statistically significant (p-value=0.077). Patients with duration of infertility of 4 to 8 years had more abnormal HSG findings (74.1%) compared to those with short duration (53.4%). This difference was statistically significant (p-value=0.003).

The study revealed that fallopian tube abnormalities were the most common affecting 99 women; 37 (37%) women with primary and 62 (63%) women with secondary infertility, followed by uterine cavity abnormalities, affecting 53 women; 16 (30%) women with primary infertility and 37 (70%) women with secondary infertility. Peritoneal cavity abnormality (Pelvic adhesion) affects 17 women; 8 (47%) women with primary and 9 (53%) women with secondary infertility. The least finding was cervical canal abnormalities, affecting 10 women; 5 (50%) women with primary and 5 (50%) women with secondary infertility respectively, as shown in Figure 2. Table 2 shows that cervical synechiea was the most common cervical canal abnormality, accounting for 3.6%

Table 3. Summary of HSG fallopian tubes findings.

Characteristic	Frequency	%	p-value (χ^2)
Normal	121	55.0	
Right occlusion	33	15.0	0.004
Left occlusion	28	12.7	
Bilateral occlusion	11	5.0	
Right hydrosalpinx	9	4.1	
Left hydrosalpinx	14	6.4	0.297
Bilateral hydrosalpinx	0	0	
Right SIN	0	0	
Left SIN	2	0.9	-
Bilateral SIN	2	0.9	
Total	220	100	

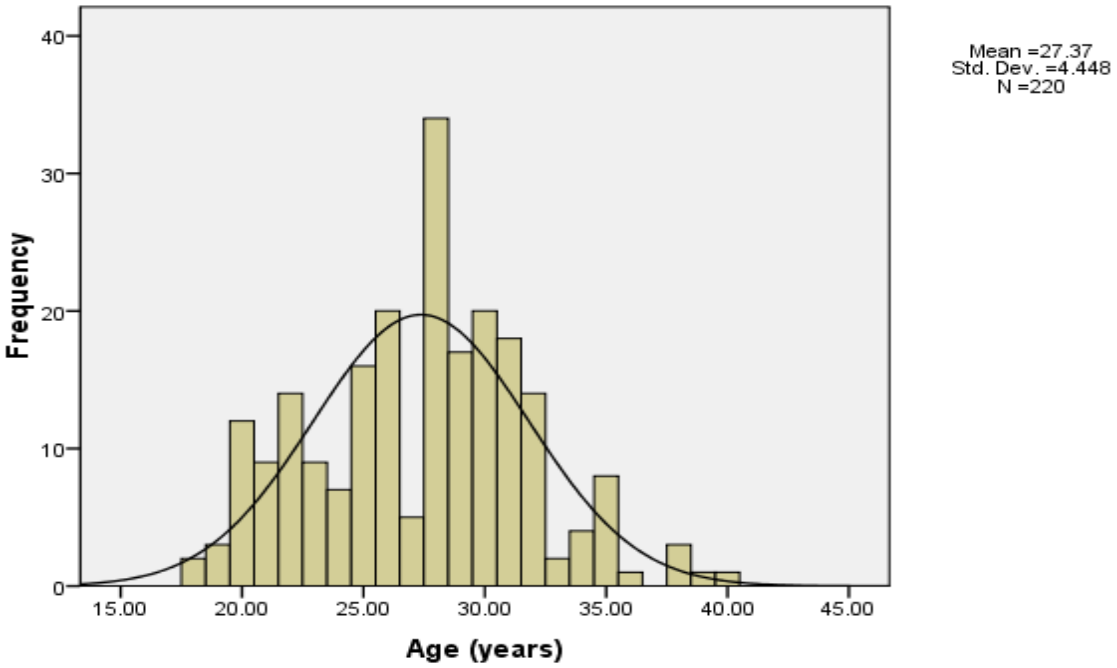

Figure 1. Histogram showing age distribution of patients.

of all the patients, with cervical dilatation as the least finding (0.9%). Table 2 also shows that uterine adhesion (Arsherman syndrome) was the most common uterine cavity abnormality seen, accounting for 11.8% of all patients. Uterine fibroid, seen as filling defects, uterine dilatation and deformity, was seen in 9.5% of the patients (Figure 3). Women who had congenital abnormality account for 2.8%, with bicornuate uterus (Figure 4) as the commonest and both unicornuate and septate uterus the least.

Table 3 shows that a total of 72 patients (32.7%) had tubal occlusion. 11 patients (5%) had bilateral tubal occlusion. Right tubal occlusion was noted in 33 patients (15%), this was slightly higher than the left tubal occlusion, which was observed in 28 patients (12.7%), but deference noted was statistically significant (p-value= 0.004). A total of 23 patients (10.5%) had hydrosalpinx. Left hydrosalpinx (Figure 5) was noted in 14 patients (6.4%), while right hydrosalpinx was noted in 9 patients (4.1%), the difference noted was not statistically significant (p- value = 0.297). A total of 4 patients (1.8%) had salpingitisisthmicalnodosa (SIN), which is usually

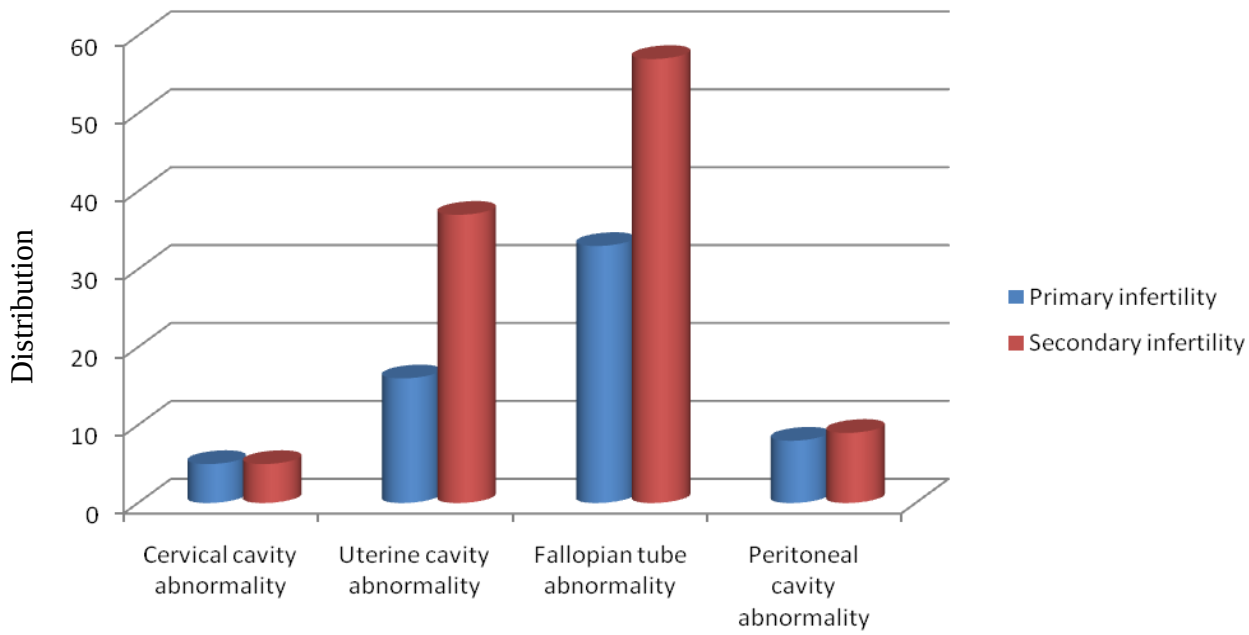

Figure 2. Distribution of uterotubal abnormalities in primary and secondary infertility.

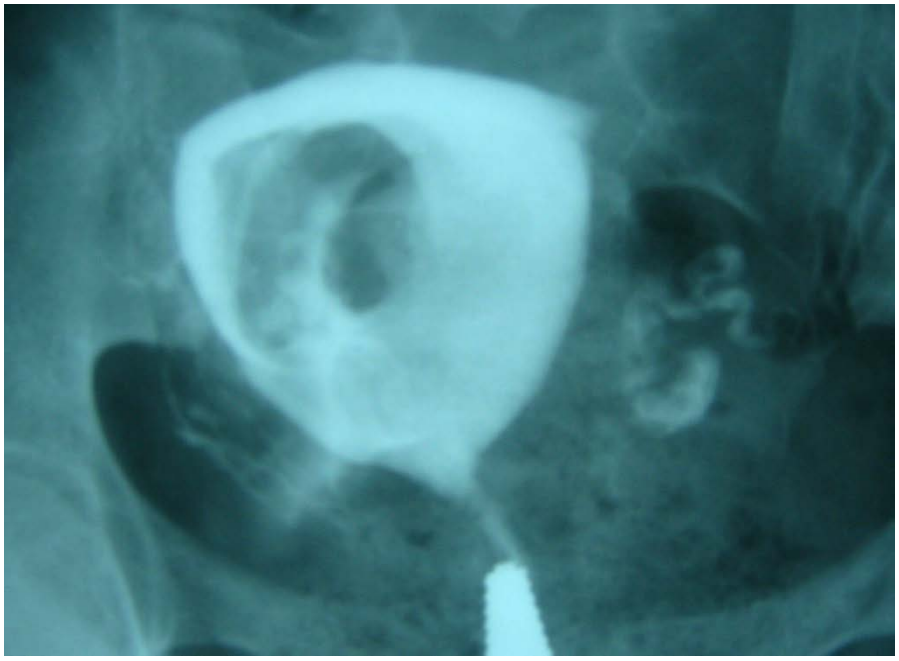

Figure 3. HSG image showing a grossly dilated uterine cavity with a filling defect due to sub mucous fibroid. The left tube is visualized and patent. The right tube is not visualized.

seen on HSG as small diverticula extending from the lumen of the tubes, 2 (0.9%) were bilateral while the remaining 2 (0.9%) had left SIN. There were 17 patients (7.7%) with pelvic adhesion, seen as loculated spill, convoluted or crowded tubes and vertical oriented tubes. Bilateral pelvic adhesion was seen in 5 patients (2.3%). Right pelvic adhesion was seen in 8 patients (3.2%) while left pelvic adhesion was seen in 4 patients (1.8%). The difference noted was statistically significant (p- value = < 0.0001).

Following further diagnostic work up, diagnostic laparoscopy was performed for 46 patients for confirmation of

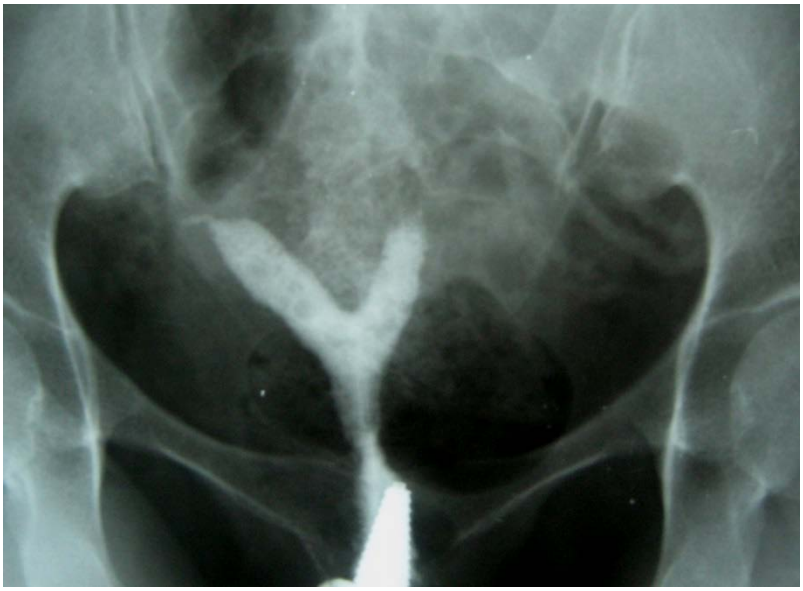

Figure 4: HSG image showing symmetrically separated uterine cavity with a single cervical canal (bicornuate unicollis uterus). Both fallopian tubes are proximally occluded.

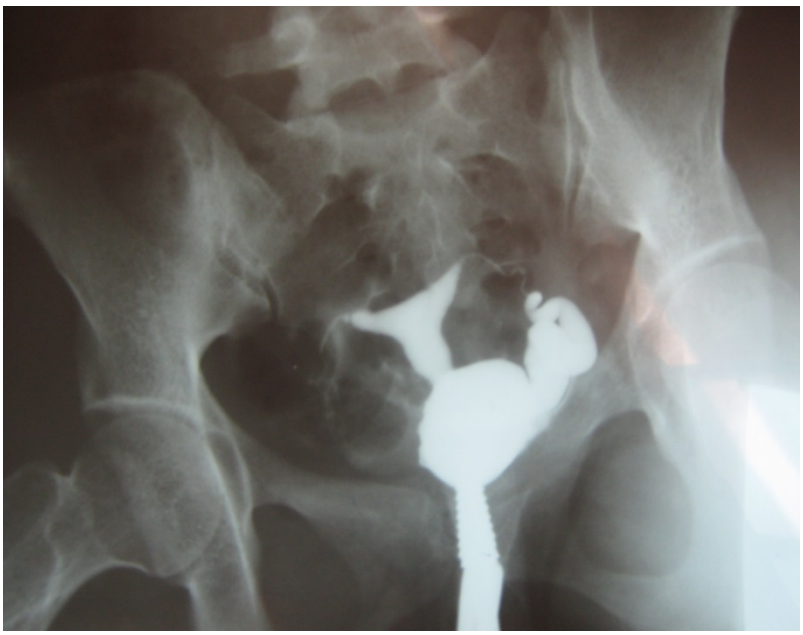

Figure 5. HSG showing dilated left fallopian tube (hydrosalpinx) without spillage of contrast medium into the peritoneal cavity. The right tube is proximally occluded.

tubal occlusions and 9 patients for confirmation of pelvic adhesions. Also, 21 patients diagnosed at HSG with intra uterine adhesions, had diagnostic and therapeutic hysteroscopy performed. Using laparoscopy with dye test and hysteroscopy as gold standards, findings were compared with HSG diagnosis. Table 4 shows that, out of the 72 women with tubal occlusion on HSG, 46 (63.89%) women had laparoscopy with dye test. HSG demonstrated unilateral tubal occlusion in 35 (76.09%) women and bilateral tubal occlusion in 11 (23.91%) women. Hydrosalpinges, suspected peritubularadhesions and fibroids were found in 5 (10.87%), 9 (19.57%), 5 (10.87%)

Table 4. Findings on hysterosalpingogram, diagnostic laparoscopy with dye test and hysteroscopy.

Variable	HSG		Laparoscopy with dye test		Hysteroscopy		Statistical tests		
	No.	%	No.	%	N0.	%	X^2	df	P value
Tubal patency									
Bilateral tubal occlusion	11	23.91	10	21.74	-	-	0.051	1	p>0.05
Unilateral tubal occlusion	35	76.09	34	73.91	-	-	0.164	1	p>0.05
Patent tube	-	-	2	4.35	-	-	-	-	-
Total	46	100.00	46	100.00	-	-	-	-	-
Endomyetrial cavity									
Intra-uterine adhesion	26	100	-	-	26	100	0.174	1	p>0.05
Others									
Hydrosalpinx/megasalpinx	5	10.87	19	41.30	-	-	7.030	1	P<0.05
Peritubular adhesions	9	19.57	17	36.96	-	-	5.212	1	P<0.05
Uterine filling defect / Fibroids	5	10.87	20	43.48	-	-	28.412	1	P<0.05

respectively. The laparoscopy with dye test also demonstrated unilateral tubal occlusion in 34 (73.91%) women and bilateral tubal occlusion in 10 (21.74) women. Some other laparoscopy findings included small uterine fibroids 20 (43.48%), Hydrosalpinges/megasalpinges 19 (41.30%), peritubal adhesions 17 (36.96%), ovarian adhesions 15 (32.61%), adhesions in pouch of Douglas 14 (30.43%), Congestion/hyperemia 7 (15.21%), ovarian cysts/masses 6 (13.04%) and omental adhesion 5 (10.87%). The difference in the findings of both tests on tubal patency was not statistically significant (p>0.05). Patients with adhesions at laparoscopy had adhesiolysis as therapeutic intervention.

All the 26 women with uterine adhesion on HSG had diagnostic hysteroscopy which confirmed all the cases. There was no difference in the findings of both tests (p>0.05). All the 26 patients with intrauterine adhesions at hysteroscopy had adhesiolysis as therapeutic intervention.

DISCUSSION

The mean age of participants in this study was 27.37 years; this was similar to the mean age of infertile women in another study by Bello (2004) in Ilorin, Nigeria. But this value is lower than that of Okafor et al. (2010) in Nnewi, southeastern Nigeria where the mean age of their study was 32.41. The difference may be due to cultural differences influencing the age at marriage. The mean duration of infertility was 4.48 years which is similar to previous study done in Nigeria (Bello, 2004). The mean duration of infertility is reported low in other study conducted by Fadare (2011). Most of the patients in this study had 4 to 8 years of infertility with majority of these patients, showing significant number of abnormalities (74%). The presence of enormous local traditional healing practices and religious believes could be an important contributory factor for the delay in presentation to health facilities.

In this study more patients had secondary infertility than those with primary infertility, which is similar to other previous studies (Akinolaet al., 2009; Watson et al., 1994). However this differs from other studies where it was found that primary infertility was commoner (Okaforet al., 2010; Obejide et al., 1986; Mesbazriet al., 2009). This higher rate of patients with secondary infertility compared to the primary infertility can be used as a crude indicator of the possible effects of pelvic inflammatory disease, post abortal sepsis and puerperal sepsis in our setting (Bello, 2004; Kiguli-Malwadde and Byanyima, 2004). In the present study, 220 patients, 72 cases (32.7%) had normal HSG findings, 148 patients had abnormal findings accounted for 67.3% of total cases. The demonstration of high abnormal findings in this study is comparable to that reported from Uganda (Baramki, 2005). The reason adduced for this could be due to the fact that ABUTH, being a tertiary hospital receives referrals from peripheral health facilities where initial evaluation of infertility causes has been done. Also most of these patients have already been seen and evaluated at ABUTH fertility clinic, hence more likely to have structural abnormalities.

From this study, cervical canal abnormalities were the least, accounting for 4.5% of all the patients, with cervical synechiae being the commonest (3.9%). This is similar to the findings of Saimaet et al. (2008). Cervical adhesion may be to due previous instrumentation, obstetric accidents or infection (Saimaet al., 2008). Congenital uterine abnormalities which are due to Mullerian ducts abnormalities during the early weeks of gestation, accounted for 2.5% of the abnormalities detected on HSG in this

study. This is lower than 3.7% reported by Bukaret et al. (2011) in Maiduguri, but higher than 1.4% reported by Josephet et al. (1978). The most common congenital uterine abnormality was bicornuate uterus 1.8%. This is in agreement with the findings of Bukar et al. (2011), where bicornuate uterus was also the commonest (1.8%). Uterine synaechia, (11.8%) was the most commonly acquired uterine pathology detected on HSG followed by uterine fibroid (9.5%). This is similar to the finding of Bukar et al. (2011), but contrast with that of Mgbor (2006), who found uterine fibroid as the leading uterine pathology. The high incidence of uterine synechia may be due to postpartum endometritis or overzealous curettage following abortion. The wide-spread use of manual vacuum aspiration for evacuation of the uterus is expected to lower the incidence of uterine synaechia and consequently the contribution of uterine synaechia to infertility in our environment (Bukar et al., 2011).

The prevalence of tubal abnormalities demonstrated in the present study was 45%, which was similar to what was reported by Bello (2004) in Ilorin, Nigeria (40%). This is much lower than that found by Akinola et al. (2009) in Lagos (61.8%). The commonest tubal abnormality found was tubal blockage (32.7%), which was similar to the report of Baramki (2005). Bilateral tubal blockage was noted in 5% of the total patients while right tubal blockage occurred in 15 % and left in 12.5% of the total patients. It may however be difficult to differentiate bilateral tubal bockage from bilateral cornual spasm or under filling from technical inadequacies. Radiographically, cornual spasm is characterized by tapering and smooth cornual margin, which is pointed or blunt and irregular in cases of occlusion (Baramki, 2005). However, the use of antispasmodics and a gentle technique was employed to minimize the effect of spasm in this study.

Hydrosalpinx is seen as a dilated convoluted tubular structure on HSG which gradually increase in size due to distal tubal occlusion (Neerja, 2001). It is a result of fallopian tubes inflammation following infections like gonococcal, chlamydial or tuberculosis of the genital tract. The fimbrial ends are eventually occluded due to adhesions leading to collection of the secretions in the lumen with gradual distension of the fallopian tube (Neerja, 2001). The incidence of hydrosalpinx (10.5%) is less in this study than similar studies done in Ilorin by Adetiloye (1988) (44.5%) and Bello (2004) (23.3%). This might be due to the conservative culture in Zaria predisposing the patients less to sexually transmitted diseases and post abortioncomplications responsible for hydrosalpinx. The lower value may also be due to the improvement in the health care delivery system over the years. A lot of researchers suggested that the presence of the appendix on the right side may predispose to increased pelvic inflammatory disease on the right side with resultant hydrosalpinx (Mesbazri et al., 2009). However in this study, the left hydrosalpinx (6.4%) was more than the right (4.1%), and therefore, the above theory does not apply.

SIN is a rare condition involving the fallopian tube due to chronic salpingitis. It is usually seen on HSG as small diverticula extending from the lumen of the tubes, involving the isthmus and associated with infertility and ectopic pregnancy (Neerja, 2001). In this study, 1.8% of the total patients had SIN. This is similar to the finding of Troell (1970) (1.1%) but less than the finding of Creasy et al. (1985) who reviewed 1,184 HSG and identified only 45 patients with SIN (3.8%). Pelvic adhesions are usually formed as a result of inflammation from PID. Adhesion disturbs the delicate anatomical relationship between the tubes and ovaries, interfering with the normal ovulation or preventing the normal capture and transport of the ovum (Neerja, 2001). Laparoscopy is the gold standard for diagnosing pelvic adhesion (Akinola et al., 2009). HSG sensitivity in diagnosing pelvic adhesion ranges from 34 to 46% (Stephen and Goldfarb, 1989). However, with Stephen and Goldfarb (1989) criteria, which includes; convoluted tubule, peritubal halo effect, vertical fallopian tube and loculated spill, as used in this study, the sensitivity of HSG can be increased to about 75% in diagnosing pelvic adhesion (Stephen and Goldfarb, 1989). In this study, patients with features of pelvic adhesions accounted for 7.7% of all infertile patients. A study conducted previously by Elsie and Byanyima (2004) in Uganda, showed that the peritubular adhesion was higher (28%) while that done by Baramki (2005) in Pakistan was lower (7%) for all patients. This high incidence of tubo-peritoneal related pathologies may be due to PID which is reported to be the most common gynaecological disease affecting many African women (Neerja, 2001; Bello, 2004). Also, non-compliance to PID treatment, which may lead to sub-acute or chronic PID with deleterious effects on the fallopian tubes, may also be a contributory factor. This indicates that pelvic inflammatory disease (PID) is still common in our environment and makes it a common cause of infertility.

In this study, it was observed that patients with secondary infertility had more pathology (49.1%) than those with primary infertility (28.2%). This is similar to previous studies which showed secondary infertile patients to have higher proportion of pathology than primary infertility patients (Bello, 2004; Kiguli-Malwadde and Byanyima, 2004). And also most pathologies were also higher among secondary than primary infertility when considering individual utero-tubal abnormalities. This may be because most patients with secondary infertility are advanced in age and may have been exposed to post- abortal and obstetric complications. In ABUTH fertility center, HSG is still the most common first-line diagnostic test to evaluate the uterine cavity, tubal patency and pelvic pathologies. Laparoscopy/ hysteroscopy is performed when tubal, uterine or pelvic pathologies are suspected or detected by HSG.

In this study, Both HSG and laparoscopy with dye test are effective in evaluating tubal patency with no significant

difference in accuracy. This is at par with findings from several studies including the works done by Snowden et al. (1984), Tsuji et al. (2009), Sakar et al. (2008). This differs from the findings of a study done in Amsterdam, Netherlands on women requiring in-vitro fertilization (Tanahatoe et al., 2008) in whom there was poor correlation between results of HSG and laparoscopy, even when HSG demonstrated bilateral tubal occlusion.

In this study, aside demonstration of tubal patency, laparoscopy with dye test was able to demonstrate far more tubal and non-tubal pathologies when compared with HSG. This is not surprising because in the former, the surgeon has direct view of the tubes, uterus, ovaries and other intra-abdominal organs. This finding is also similar with other reports from other similar studies such as the work done by Sakar et al. (2008) as well as La Sala et al. (1987). These tubal and non-tubal findings besides demonstration of tubal blockage, may reveal the actual causes of infertility in a patient, hence, laparoscopy is very essential in management of infertility especially in patients with suspected tubal pathology or those with unexplained infertility.

In the current study, both HSG and hysteroscopy are also effective in evaluating endometrial adhesion with no difference in accuracy. This is in agreement with previous study by Preutthipan and Linasmita (2003). The high accuracy of HSG in assessing tubal patency in this study could be ascribed to the use of IV Hyoscine-N-Butybromide (20mg) which prevents tubal spasm during HSG (Baramki, 2005).

Conclusion

Both HSG and diagnostic laparoscopy are effective in evaluating tubal patency with no significant difference in accuracy. Also both HSG and hysteroscopy are effective in evaluating intrauterine adhesions with no difference in accuracy.

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Conflict of interest

The authors have not declared any conflict of interest.

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Full Length Research Paper

Endosymbiont bacterium *Wolbachia*: Emerged as a weapon in the war against mosquito-borne diseases

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Because of climate change and failure of the existing methods of control of vector borne diseases and vector are increasing. Mosquito species are the main vectors of human pathogens causing malaria, dengue, filariasis, chikungunya, yellow fever and West Nile. There are no well-organized methods and tools of controls of vector and vector borne diseases, since no efficient vaccines or drugs are available. Despite years of intense effort to control them, many of these diseases are increasing in prevalence, geographical distribution and severity, and options to control them are limited. Currently, efforts focused on the control of vector populations. During recent years, the endosymbiont bacterium has been well-documented and has led to suggestions that these could be used to control pests and therefore diseases. *Wolbachia* is perhaps the most renowned insect symbiont, primarily due to its ability to manipulate insect reproduction and to interfere with major human pathogens therefore providing new avenues for pest control. *Wolbachia* are common intracellular bacteria that are found in arthropods and nematodes. These alphaproteobacteria endosymbionts are transmitted vertically through host eggs and alter host biology in diverse ways, including the induction of reproductive manipulations, such as feminization, parthenogenesis, male killing and sperm–egg incompatibility. *Wolbachia* strains can invade and sustain themselves in mosquito populations, reduce adult lifespan, affect mosquito reproduction and interfere with pathogen replication. *Wolbachia* can also provide direct fitness benefits to their hosts by affecting nutrition and development, influencing fecundity or oogenesis and providing resistance to pathogens. For instance, infection of *Anopheles gambiae* with both *w*MelPop and *w*AlbB reduced the oocyst burden of *Plasmodium falciparum*, compared to uninfected control mosquitoes. In addition, similar study observed that the *w*MelPop strain inhibited development of *Plasmodium berghei*; however, the *w*AlbB strain was found to enhance development of *P. berghei*.

Key words: Malaria, *Aedes aegypti*, Chikungunya, dengue, drosophila, *Wolbachia pipientis,* vector-borne diseases.

INTRODUCTION

Vector-borne diseases occur in more than 100 countries, mainly within the tropics, with the annual, global death

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rate in millions (McGraw and O'Neill, 2013). A variety of vector-borne diseases, which often coexist in the same environments,impose a heavy burden on human populations, in developing countries mainly in tropical and subtropical zones. Besides the direct human suffering they cause, vector-borne diseases are also a significant obstacle to socioeconomic development (KKeiser et al., 2005). Insect-borne diseases, mostly those transmitted by mosquitoes, are among the most important causes of mortality and morbidity in humans (World Health Organization, 2008). The occurrence of mosquito-borne diseases such as malaria, lymphatic filariasis, dengue fever, Chikungunya, West Nile virus, yellow fever and Japanese encephalitisare rise annually due to human travel, rapid urbanization and failures of preventative public-health measures (Adams and Kapan, 2009).

Recent study reported that Vector borne diseases (VBD) are increasing because of the climate change and failure of the existing methods of vector control and vector borne diseases. Moreover, a sudden increase of VBDs is reported due to many factors like insecticide resistant vector population, drug resistant parasite population and lack of effective vaccines against the VBDs, and thus insecticides are no longer a sustainable control method of vector and vector-borne diseases due to environmental pollution, public health hazard and insecticide resistant vector population (Gupta et al., 2012). Despite the existence of a variety of vector control measures, disease incidence is usually growing, and therefore there is an urgent need to develop new and effective control approaches (McGraw and O'Neill, 2013), because no effective vaccines or treatments against vector bore diseases exist (Wilder et al., 2010) and control methods are failing to prevent the global increase in the incidence of the disease (Ricci et al., 2011a). These new and effective strategies should be used in combination with existing control techniques, and in this context the bacterium Wolbachia pipientis has proven to be a promising option, given its ability to limit pathogen growth in numerous dissimilar mosquito pathogen combinations (Kambris et al., 2009; Bian et al., 2010; Glaser and Meola, 2010; Bian et al., 2013), and currently being applied in the field in Australia, Vietnam and Indonesia.

Wolbachia was believed to be members of an uncommon and unimportant bacteria genus until the early 1990s. However, after the introduction of molecular typing techniques *Wolbachia* were found to be prevalent and familiar in arthropods filarial nematodes. A recent meta-analysis estimated that more than 65% of bug species harbor *Wolbachia*, making it among the most plentiful intracellular bacteria genus so far revealed, infecting at least 10 insect species alone (Hilgenboecker et al. 2008).

Wolbachia are members of the order Rickettsiales, a dissimilar group of intracellular bacteria having parasitic, mutualistic and commensal relationships with their hosts. Although, the related genera (like *Anaplasma, Ehrlichia* and *Rickettsia*) infects (Werren et al. 1994), *Wolbachia* do not routinely infect vertebrates. *Wolbachia* have attracted substantial interest in the past decade primarily because of their huge abundance, fascinating effects on hosts, which ranges from reproductive manipulation to mutualism, and potential applications in pest and vector born diseases control (Werren et al., 1994). *Wolbachia* is a vertically-transmitted bacterial endosymbiont of arthropods that is able to influence its host's reproductive system and thus spread quickly through wild populations (Werren et al., 2008). *Wolbachia* was originally identified in the ovaries of the mosquito *Culex pipiens* (Hertig and Wolbach, 1924), and recent studies have estimated that 40% of terrestrial arthropod species are infected with *wolbachia* (Zug and Hammerstein, 012). Based on Multi-Locus Sequence Typing (MLST) (Baldo et al., 2006), *Wolbachia* is recently divided into eight monophyletic "supergroup" lineages (A-H) (Lo et al., 2007), with new hosts being discovered constantly (Wang et al., 2010; Vasquez et al., 2011).

METHODOLOGY

Qualitative method was used to evaluate the significance and problems related to vector born diseases. Authors reviewed different journals, reports (WHO recommendations), and related documents. Accessible materials were browsed from internet sources which were published from 1924 to 2014. The following sites and search engines were used: HINARI, Medline (Pubmed), Google scholar, and Science Direct. The selection process is as illustrated in Figure 1.

WOLBACHIA INVASION OF MOSQUITO POPULATIONS AND HOST BIOLOGY

A study in India demonstrated that paratransgenic based approach can be used effectively, where dengue, chikungunya, malaria and filariosis are prevalent (Gupta et al., 2012). *Wolbachia* are common intracellular bacteria that are found in many terrestrial arthropodsand nematodes. These alpha proteobacteria endosymbionts are transmitted vertically through host eggs and alter host biology in different ways, including the induction of reproductive manipulations, such as feminization, parthenogenesis, male killing and sperm–egg incompatibility. They can also move horizontally across species boundaries, resulting in a widespread and global distribution in diverse invertebrate hosts (Werren et al., 2008). *Wolbachia* are highly adapted for living within invertebrate cells, which probably partly explains their wide distribution (Serbus and Sullivan, 2007).

A similar study reported that the effects of *Wolbachia* infection for example feminization of genetic males; parthenogenetic induction, which results in the development of unfertilized eggs; the killing of male progeny from infected females; andcytoplasmic incompatibility (CI) also called sperm–egg incompatibility, and collectively, these strategies are referred to as reproductive parasitism.

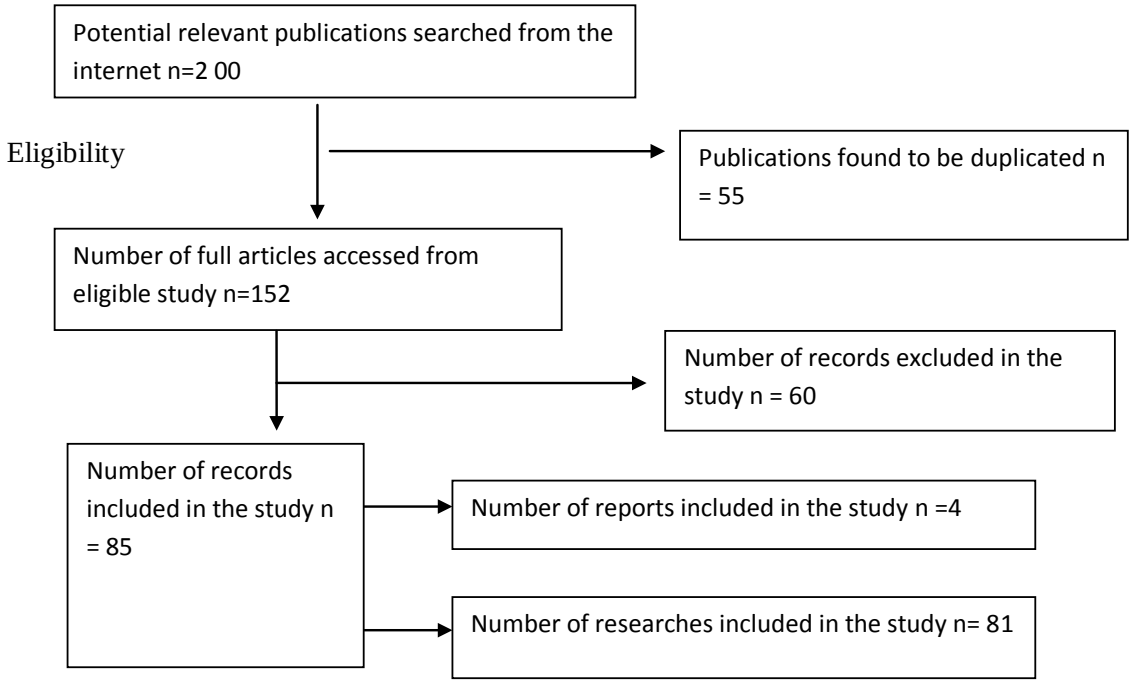

Figure 1. Flow diagram showing reviewed documents.

Furthermore, *Wolbachia* have also evolved mutualistic interactions with their filarial hosts, and show a range of other host effects (Serbus and Sullivan, 2007). Different up to date studies showed that the symbiotic bacterium *Wolbachia* is an attractive agent for vector-borne pathogen control. The ability of *Wolbachia* to manipulate host reproduction and spread into arthropod populations (Werren et al., 2008), together with the recently recognized ability to inhibit diverse pathogens (Hedges et al., 2008; Kambris et al., 2009; Moreira et al., 2009b; Kambris et al., 2010; Hughes et al., 2011), open an opportunity for its use in controlling vector and vector-borne disease. Numerous *Wolbachia* based control strategies are being investigated (Iturbe-Ormaetxe et al., 2011; McGraw nd O'Neill, 2013; Bourtzis et al., 2014), with some studies having progressed to field trials (Walker et al., 2011; Hoffmann et al., 2011).

The endosymbiont bacterium *Wolbachia* influences host physiology positively (Brownlie et al., 2009; Kambris et al., 2010), which is recognized for parasitism that alters host reproductive success, including cytoplasmic incompatibility (CI) (Werren et al., 2008). CI is the most studied reproductive modification induced by *Wolbachia* and results in embryonic lethality when uninfected females are crossed with *Wolbachia* infected males. In a population composed of infected and uninfected individuals, only infected females can mate successfully with infected and uninfected males (Werren et al., 2008). When two *Wolbachia* strains exist in a population, bidirectional CI can result in incompatibility between individuals carrying different strains, while individual females infected with multiple strains (superinfected) can mate with all males and produce infected progeny (Engelstadter et al., 2009). In both CI types, *Wolbachia* is expected to sweep through populations due to higher reproductive fitness because of the higher proportion of successful matting's between infected or super infected females relative to the uninfected ones. However, not all *Wolbachia* strains cause CI and strength of CI expression (penetrance) can be altered by *Wolbachia* density or transmission efficiency (maternal transmission fidelity) (Unckless et al., 2009).

Given the influence of *Wolbachia* on host fitness, the potential impact of *Wolbachia* on host population genetic variability and geographical patterns is substantial. Since *Wolbachia* is maternally transmitted, other maternally transmitted organelle (example, mitochondria) hitchhike with *Wolbachia* infections (Turelli et al., 1992; Rasgon et al., 2006). Even though simulations indicate that CI-based spread of *Wolbachia* sweeps are more likely to involve repeated initial infections via horizontal transmission (Egas et al., 2002; Jansen et al., 2008), most studies of CI associated *Wolbachia* sweeps find it asso-ciated with low mitochondrial DNA (mtDNA) variation and with many hosts infected (Nunes et al., 2008). Theoretical models suggest that host dispersal or migration, and genetic background (Duron et al., 2007; Mouton et al., 2007) can influence these sweeps (Keeling et al., 2003; Telschow et al., 2005; Flor et al., 2007; Engelstadter et al., 2009). Factors that control *Wolbachia* density, such as nutrient availability or temperature (Hurst

et al., 2000; Dutton and Sinkins, 2004), indirectly influence CI-based sweeps, because at high, *Wolbachia* densities maternal transmission fidelity and CI expression are stronger than those at low *Wolbachia* densities. Although the mechanism is not well known, *Wolbachia*-induced CI has received considerable attention as a mechanism to control insect vectors and diseases. *Wolbachia* is responsible for inducing a number of reproductive modifications that enables its spread and maintenance in natural populations (Saridaki and Bourtzis, 2009; Guruprasad et al., 2013).

Recently, there has been a considerable raise in *Wolbachia* research related to the interactions of *Wolbachia* with its hosts and its impact on parasite transmission. Fruit fly *Drosophila melanogaster Wolbachia* strains can invade and sustain themselves in mosquito populations, reduce adult lifespan, affect mosquito reproduction and interfere with pathogen replication. Such endosymbiotic bacterial strains have been introduced in *Aedesaegypti* (*Ae. aegypti*) mosquito populations to reduce their life span, thereby reducing the extrinsic incubation period. The other prospect of exploiting *Wolbachia* is using its ability to interfere with viruses and parasites. *Wolbachia* is known to interact with a wider range of pathogens in transfected mosquitoes including dengue and chikungunya viruses (Brelsfoard and Dobson, 2011).

A major advantage of *Wolbachia*-based control approach for mosquitoes is that CI acts as a self-spreading mechanism for *Wolbachia* to rapidly invade populations from the release of relatively small numbers of individuals. *Wolbachia* provides a biological method to manipulate mosquito populations and reduce disease transmission (Iturbe-Ormaetxe et al., 2011). Since Wolbachia based control methods are mostly environment-friendly than insecticide-based techniques, findings have encouraged researchers to aid in the control of mosquito-transmitted diseases. Similarly, identical Ae.*aegypti* lines infected and uninfected with *w*MelPopwolbacha strain were compared to determine whether differences in gene expression between the two lines were related with the life-shortening phenotype, *w*MelPop induces an up-regulation of the mosquito's innate immune system and that its presence inhibits the development of filarial nematodes in the mosquito. Once again, *w*MelPop could be used in control programs to eradicate lymphatic filariasis and other MBDs (Zielinski et al., 2008).

WOLBACHIA TRANSFER INTO *AEDES AEGYPTI* MOSQUITOES

Dengue fever is the most important arboviral disease in humans; 40% of the population of the world in more than 100 countries is at risk of infection and an estimated 50 to 100 million cases occur annually (Guzman and Kouri, 2002; WHO, 2009). Dengue (DENV) is primarily transmitted by the infectious bite of a female *A. aegypti* mosquito and to a much lesser extent, *Aedes albopictu* (Lambrechts et al., 2010).

Wolbachia infections are relatively common in mosquitoes (Kittayapong et al., 2000) including *C. pipiens* (Yeap et al., 2010), *quinquefasciatus*, *Aedesfluviatilis* (Moreira et al., 2009b) and *Aedes albopictus* (Moreira et al., 2009a). The main vectors for dengue fever (*A. aegypti*) and malaria (*Anopheles* spp.) are not naturally infected by *Wolbachia.* Approaches that use *Wolbachia* for the control of diseases transmitted by uninfected, naive insects rely on the successful establishment of stable *Wolbachia* infections, usually by embryonic microinjection of *Wolbachia*-infected cytoplasm or *Wolbachia* purified from infected insect hosts. To create stably transinfected lines, embryo injections must target the region near the pole cells in pre-blastoderm embryos to incorporate *Wolbachia* into the developing germline and favour the transmission of *Wolbachia* to offspring. Several *Wolbachia* strains have been transferred across phylogenetically distant insects and, importantly, the phenotypes induced by these strains in their native hosts are generally also expressed in the newly infected hosts (Iturb et al., 2011). *Wolbachia* transinfection experiments are more likely to be successful when the donor and recipient organisms are closely related. In line with this, the transfer of *w*MelPop from its natural host, *D. melanogaster*, into the dengue fever vector *A. aegypti*was achieved in our laboratory after *Wolbachia* was first maintained by continuous passage in *A. albopictus in vitro* cell culture for almost 4 years (McMeniman et al., 2009).

Wolbachia adapted to a mosquito intracellular environment, facilitating transinfection *in vivo*. After microinjection of thousands of *A. aegypti* embryos, two stable *w*MelPop-CLA (cell-line-adapted) lines with maternal transmission rates of approximately 100% were generated (McMeniman et al., 2009). *w*MelPop-CLA-infected mosquitoes showed an approximately 50% reduction in adult lifespan, compared with their uninfected counterparts (McMeniman et al., 2009). The halving of adult mosquito lifespan and the high *Wolbachia* maternal transmission rates were also maintained in more genetically diverse outbred mosquitoes, and larval nutrition did not affect the life-shortening ability of the *w*MelPop-CLAstrain (Bian et al., 2010; Yeap et al., 2010). The *w*MelPop-CLA infection is widespread in *A. aegypti* tissues, with high bacterial densities in the head (brain and ommatidia), thorax (salivary glands, muscle) and abdomen (fat tissue, reproductive tissues and Malphigian tubules) (Moreira et al., 2009). Wide distribution across tissues has been found in other transinfected mosquitoes, such as *A. aegypti* infected with the *w*AlbB strain from *A. albopictus* (Bian et al., 2010). By using quantitative Polymerase Chain Reaction (PCR) and Western blot analyses, this strain was also found in

reproductive tissues, midgut, muscles and heads, in both native *A. albopictus* (Dobson et al., 1999) and the transinfected *A. aegypti* (Bian et al., 2010), although the densities are not as high as those found in *A. aegypti* infected with *w*MelPop-CLA.

WOLBACHIA INTERFERENCE WITH VIRUSES AND PARASITES

A key element in the use of *Wolbachia* for the control of insect-borne disease has been the discovery that some *Wolbachia* strains can interfere with insect viruses in *Drosophila* and human pathogens in mosquitoes. Interestingly, the presence of *Wolbachia* interferes with a wider range of pathogens in transinfected mosquitoes including nematodes and bacteria (Kambris et al., 2009), viruses such as DENV and Chikungunya (Moreira et al., 2009a; Bian et al., 2010), as well as the avian and rodent malaria parasites *Plasmodium gallinaceum* (Moreira et al., 2009b) and *P. berghei* (Kambris et al., 2010). Natural *Wolbachia* strains that infect mosquitoes have also been shown to induce resistance to viruses as in *Culex quinquefasciatus* mosquitoes, that are resistant to West Nile virus (Glaser and Meola, 2010) although, this resistance seems less pronounced in comparison to transinfected *Wolbachia* strains such as *w*MelPop-CLA (Moreira et al., 2009a). The mechanisms by which some *Wolbachia* strains interfere with a variety of pathogens remain unclear. One assumption is that pathogen interference is partly mediated by the induction of antimicrobial peptides and pre-activation of the innate immune response in the insect (Kambris et al., 2009; Moreira et al., 2009b; Kambris et al., 2010). The presence of *w*MelPop-CLA *Wolbachia* in *A. aegypti* induced the expression of several immune effect or molecules, including cecropin, defensin, thio-ester containing proteins and C-type lectins (Moreira et al., 2009b). When the *w*MelPop strain was transiently injected into adult *Anopheles gambiae*, several immune genes were upregulated, as shown by whole-genome arrays (Kambris et al., 2009), resulting in the inhibition of *Plasmodium* development (Kambris et al., 2009).

WOLBACHIA INTERFERES WITH PLASMODIUM PARASITES

Malaria is a disease caused by infection of *Plasmodium* protozoan parasites by the bite of anopheline mosquitoes which results in an estimated 1 to 2 million deaths per year, taking a dramatic toll on health and socioeconomic development in affected areas (World Health Organization, 2008). Another similar study also indicated that malaria-transmitting anopheles mosquitoes are the deadliest animals on this planet, causing the death of more than 600,000 people each year and endangering the lives of half of the world's population (World Health Organization. World Malaria Report: World Health Organization 2013). As a result, malaria remains one of the most critical public health challenges for Africa despite intense national and international efforts (WHO, 2012).

As different researchers point out that the current insecticide-based control strategies to stop malaria transmission by targeting the mosquito vector which are limited by the rapid spread of insecticide resistance (Ranson et al., 2011). Moreover, insecticide-based control strategies target only indoor feeding and resting populations, with the use of insecticide treated bed nets and the application of indoor residual sprays, respectively. The use of *Wolbachia* endosymbionts has been proposed as an alternative to chemical strategies because of the ability of *Wolbachia* bacteria to rapidly invade insect populations through CI, (Walker and Moreira, 2011) and successful *Wolbachia* invasions in field settings have been demonstrated in the case of the dengue and yellow fever vector Aedes aegypti (Hoffmann et al., 2011).

Recent proof have shown that *Wolbachia* infections of anopheles vectors limit the development of the plasmodium parasites that causes malaria (Kambris et al., 2010; Hughes et al., 2011; Bian et al., 2013; Murdock et al., 2014) makes these bacteria a particularly attractive tool for the control of both endophagic and exophagicanophelines mosquito. Long-standing limitations concerning the introduction of *Wolbachia* into laboratory colonies of anopheles mosquitoes have been recently overcome (Bian et al., 2013); however, the usefulness of this system for the control of anopheles populations has been undermined by the apparent absence of natural infections. Indeed, Wolbachia strains have been detected in many insects (Hilgenboecker et al., 2008).

A recent study confirmed that *P. falciparum* development in Anopheles *gambiae* (*A. gambiae*) is suppressed transiently as a result of *Wolbachia* infection. This reproductive parasite is known to indirectly support and up-regulate the insect-host immune system and suppress the pathogen (Pinto et al., 2012). *Wolbachia* limits the spread of numerous human pathogensby manipulating their reproduction and immunity. In anopheles mosquitoes, experimental *Wolbachia* infections can reduce plasmodium numbers in the laboratory; however, natural *Wolbachia* infections in field anophelines have never been reported. A study in Burkina Faso, West Africa has shown evidence of *Wolbachia* infections in anopheles gambiae. Sequencing of the 16S rRNA gene identified *Wolbachia* sequences in both female and male germlines, and also determined that these sequences are vertically transmitted from mother to offspring. Whole-genome sequencing of positive samples suggests that the genetic material identified in *A. gambiae* belongs to a novel *Wolbachia* strain related to but distinct infecting

other arthropods. The evidence of *Wolbachia* infections in natural anopheles populations promotes further investigations on the possible use of natural *Wolbachia* anopheles associations to limit malaria transmission (Baldini et al., 2014).

Interestingly, *Wolbachia* can protect insects from pathogens and limit their ability to transmit mosquito-borne pathogens (Iturbe et al., 2011). This effect was first observed where naturally *Wolbachia* infected *Drosophila* were protected against fungal and viral pathogens (Panteleev et al., 2007). More complex pathogens are also susceptible to *Wolbachia* mediated pathogen interference. *w*MelPop infected *A. aegypti* has a reduced capacity to transmit *Brugiapahangi* (a rodent filarial model) (Kambris et al., 2009; van den Hurk et al., 2012) and *P. gallinaceum* (avian malaria). Importantly, it shows the inhibition phenotype transfers to *Plasmodium* species of human relevance. Transient somatic infection of *A. gambiae* with both *w*MelPop and *w*AlbB reduced the oocyst burden of *P. falciparum*, the major causative agent of human malaria, compared to uninfected control mosquitoes (Hughes et al., 2011).

A similar study observed that the *w*MelPop strain inhibited the development of *Plasmodium berghei* and the mouse malaria model; however, the *w*AlbB strain was found to enhance development of *P. berghei* (Hughes et al., 2012). Recently, symbiont-mediated refractoriness to *Plasmodium* was also observed in *A. stephensi* artificially-infected with a stable *Wolbachia* infection (Bian et al., 2013). In particular, it was shown that the *w*AlbB infection can significantly inhibit *P. falciparum* infection at both oocyst and sporozoite stages (Bian et al., 2013). Interestingly, the *w*Pip strain was seen to protect *C. pipiens* mosquitoes against *Plasmodium relictum* induced mortality, increasing the lifespan of *Wolbachia* infected mosquitoes (Zélé et al., 2012). These data suggest that the pathogen protection phenotype is dependent on the specific *Wolbachia* parasite combination and serving as a warning that not all host *Wolbachia* combinations will retard parasite development.

Nematode associated *Wolbachia* show a general concordance between the phylogeny of the bacteria and the phylogeny of their hosts, and all these *Wolbachia* have evolved mutualisms with their hosts. This pattern is also found with many other vertically inherited endosymbionts, such as *Buchnera aphidicola*, the obligate intracellular symbionts of aphids (Funk et al., 2000). By contrast, *Wolbachia* that participate in symbiotic relationships with arthropods have a range of phenotypic effects on their hosts, and generally behave as reproductive parasites. There is no concordance between the phylogeny of arthropod *Wolbachia* and the phylogeny of their hosts, which is an indicative of extensive lateral movement of *Wolbachia* between host species. Furthermore, resolving the relationships between strains is further complicated by extensive recombination, even from strains among some super groups (Baldo et al., 2006; Baldo and Werren, 2007; Hilgenboecker et al., 2008).

WOLBACHIA INHIBITS DENGUE AND CHIKUNGUNYA VIRUS REPLICATION IN MOSQUITOES

Evidence from several recent studies indicates that a strain of life-shortening *Wolbachia* has been detected in the fruit fly *Drosophila*. This virulent *Wolbachia* strain wMelpop is responsible for the shortening of life span in *D. melanogaster* (Min and Benzer, 1997). In *Drosophila*, the wMelPop and another closely related *Wolbachia* strains have the ability of protecting against RNA virus infection by delaying the mortality of flies infected with a range of pathogenic viruses (Hedges et al., 2008; Teixeira et al., 2008). The *Wolbachia* wMelpop infection in *D. melanogaster* induces antiviral response to the *Drosophila* C virus in their hosts, cricket paralysis, Nora and Flock House viruses (Osborne et al., 2009), West Nile virus (Glaser and Meola, 2010), as well as the fungus *Beauveriabassiana* (Panteleev et al., 2007). These observations in *Drosophila* have made researchers to introduce this bacterial strain into the dengue virus mosquito vector *A. aegypti* artificially. The introduction of walbB strain reduces the proliferation of dengue virus when compared with uninfected mosquito population. The *Wolbachia* strain not only reduced the virus replication but also reduced the adult life span. The life-shortening *Wolbachia* exerts its effect by altering the extrinsic incubation period of dengue virus, thereby inhibiting its transmission to new host. Meanwhile life-shortening *Wolbachia* may offer a new technology to control the chikungunya virus as well. These results may offer a potential new method to control vector-borne diseases like dengue and chikungunya virus from *A. Aegypti* (Moreira et al., 2009).

Mosquitoes infected with *w*Mel showed significantly reduced rates of chikungunya infection and dissemination to the salivary glands compared to controls, but only in the oral exposure experiments. Chikungunya also showed limited dissemination in *w*MelPop-CLA-infected mosquitoes following oral exposure (Moreira et al., 2009), suggesting that both strains of *Wolbachia* may be useful candidates for release in chikungunya control programs. By contrast, yellow fever (YFV) was much less likely to infect and disseminate in *A. aegypti* infected with *w*MelPop-CLA compared to *w*Mel strains. The virus was also less likely to replicate in *w*MelPop-CLA infected mosquitoes, with very high virus loads detected in *w*Mel-infected *A. aegypti*.

These experiments suggest that *w*MelPop-CLA infected mosquitoes may be the best candidates for YFV biocontrol programs, but were unable to determine the extent of virus replication following oral exposure rather than intrathoracic inoculation. Because virus inhibition with some *Wolbachia*-virus combinations does not

appear to be complete, it is essential that epidemiological models be utilized to establish the threshold virus inhibition necessary to minimize and prevent transmission in the field (van den Hurk, 2012). The chikungunya strain was isolated from a patient visiting Melbourne, Australia in 2006 and contained the alanine to valine mutation in the membrane fusion glycoprotein E1 gene (E1-A226V) that has been linked to increased infectivity in mosquitoes, especially *A. Albopictus* (Druce et al., 2007).

WOLBACHIA PIPIENTIS AND DISEASE CONTROL

The potential application of the symbiotic bacteria *Wolbachia pipientis* to the control of mosquito-borne diseases has emerged as a recent addition to the arsenal of weapons against mosquitoes. It is more environmentally friendly than insecticide-based approaches and more cost effective. In recent years, there is an interest in *Wolbachia bacterium* as a means by which to control insect-transmitted diseases. However, *Wolbachia* induced cytoplasmic CI was proposed as a tool for *Culex* mosquito control as early as 1967 (Laven, 1967) and there were trials to eradicate mosquitoes in India in the 1970s (Curtis and Adak, 1974), but although there has been some field testing, it has never been operationally implemented. *Wolbachia,* the most-common known endosymbiotic microbe in the biosphere, is thought to infect up to 76% of the estimated 2 to 5 million insect species on earth (Hilgenboecker et al., 2008). The success of these small (0.5 to 1µm) intracellular bacteria has been attributed to their ability to induce a series of reproductive distortions in their hosts to increase the reproductive success of infected females, thus enhancing the maternal transmission of *Wolbachia* (Werren et al., 2008). These traits include transforming genotypic males into phenotypic females, modifying male sperm so that females cannot produce progeny unless they mate with a male infected with the same strain of *Wolbachia*, or inducing the parthenogenetic reproduction of females (Stouthamer et al., 1999).

FITNESS OF *WOLBACHIA* INFECTED MOSQUITOES

Wolbachia can also provide direct fitness benefits to their hosts by affecting nutrition and development (Brownlie et al., 2009; Hosokawa et al., 2010), influencing fecundity (Aleksandrov et al., 2007) or oogenesis (Dedeine et al., 2001) and providing resistance to pathogens (Hedges et al., 2008; Moreira et al., 2009; Osborne et al., 2009; Bian et al., 2010; Glaser and Meola, 2010; Kambris et al., 2010). *Wolbachia* infected mosquitoes can only spread and invade uninfected mosquito populations if the fitness cost of infection is less than the fitness advantage that CI provides for the infection to spread. Pathogen protection might also provide a fitness advantage to *Wolbachia* infected mosquitoes that will assist their spread in the field. Apart from the reduction in lifespan, some of the fitness effects induced by the *w*MelPop-CLA infection in *A. aegypti* include an increase of metabolic rate and activity in the mosquito (Evans et al., 2009), and a fecundity cost. The latter is detected as a steady reduction in hatch rates after the first gonothropic cycle, probably due to an impaired ability to feed as the mosquitoes age (Turley et al., 2009). Another significant effect of *w*MelPop-CLA infection in *A. aegypti* is the reduction of egg survival during periods of embryonic quiescence (McMeniman and O'Neill, 2010). This might be a desired control mechanism for population suppression in areas with pronounced wet/dry seasonality, by preventing the next generation of mosquitoes from hatching after the dry season.

The ability of mosquitoes infected with *w*MelPop-CLA to feed on human hosts has been tested by looking at the volume of blood they have ingested, their ability to probe successfully, and other aspects of their biting behavior (Moreira et al., 2009). *Wolbachia* does not affect the response time of mosquitoes to humans, but its presence reduces the number and size of blood meals taken. *w*MelPop-CLA *Wolbachia* also induced behavioural changes in old mosquitoes termed 'shaky' or 'bendy', in which the proboscis bends and is unable to pierce the skin; 65% of 35 day old insects showed the bendy phenotype (Turley et al., 2009). *Wolbachia* infected *A. aegypti*produce smaller volumes of saliva, which contain the same levels of the anti-platelet-aggregation enzyme and apyrase, as uninfected mosquitoes (Moreira et al., (2009).

Despite the ability of the *w*MelPop-CLA strain to induce strong CI and interfere with dengue virus (DENV) replication in transinfected *A. Aegypti* mosquitoes, the fitness effects produced in its host might be counterproductive to, or even completely block, the establishment of this strain in natural populations of mosquitoes (Turelli, 2010). Alternative, less-virulent strains might therefore be required. In *Drosophila*, viral interference is induced by several *Wolbachia* strains that are closely related to *w*MelPop (Hedges et al., 2008; Osborne et al., 2009) suggesting non-life-shortening strains with more desirable invasion characteristics which would also affect transmission of dengue fever.

Although not related with this review, the wicker hamomyces anomalus yeast, which has been indicated as a symbiont of some mosquito vector species, has been found in the midgut and reproductive organs of the host (Ricci et al., 2011b). This mosquito symbiont can be cultured in cell free media and thus may be a good candidate for the expression of effect or molecules in the midgut of mosquito vectors. A recent study describes the use of the transgenic *Metarhizium anisopliae* fungus to inhibit malaria transmission, abolishing parasite development within the mosquito (Ricci et al., 2011). Interestingly,

another study investigates a bacterium of the genus Chromobacterium (Csp_P), which was isolated from the midgut of field-caught Aedesaegypti. It is reported that Csp_P can effectively colonize the mosquito midgut when introduced through an artificial nectar meal, and it also inhibits the growth of other members of the midgutmicrobiota. In addition, Csp_P colonization of the midgut tissue activates mosquito immune responses, and Csp_P exposure dramatically reduces the survival of both the larval and adult stages. Importantly, ingestion of *Csp_P* by the mosquito significantly reduces its susceptibility to *P. falciparum* and dengue virus infection, thus compromising the mosquito's vector competence. The anti-pathogen and entomopathogenic properties of *Csp_P* render it a potential candidate for the development of malaria and dengue control strategies (Ramirez et al., 2014).

CONCLUSION

The ability of some *Wolbachia* strains to reduce the lifespan of *A. aegypti*, invade mosquito populations through the induction of CI in particular, interfere with the replication of a variety of pathogens, which has placed this bacterium at the frontline of new approaches targeting mosquito-borne diseases in an environmentally friendly manner. During the last two decades, surprising progress has been achieved in the field of *Wolbachia* symbiosis. The prevalence and diversity of the symbiont has been studied in all major classes of insects including mosquito genera that are known to contain major disease vector species such as *Aedes*, *Anopheles* and *Culex* genera. *Aedes* (but not *A. aegypti*) and *Culex* mosquito species were found to be naturally-infected. The *Wolbachia* induced extended phenoltypes, most notably cytoplasmic incompatibility and pathogen interference, and other symbiont effects on naturally-infected and transinfected species have been intensively studied, resulting in the transfer of *Wolbachia* research from the laboratory to the field.

Anopheles species, naturally uninfected, have been found reluctant to support *Wolbachia* transinfections until very recently. Recent study reported that *A. stephensi* can support the *w*AlbB *Wolbachia* strain, can express CI and block pathogen transmission (Bian et al., 2013). This is a major breakthrough which opens the way for the application of *Wolbachia* based approaches for the control of *Anopheles* mosquitoes and malaria. However, it should be noted that in many malaria endemic areas, multiple malaria vectors and genotypes thereof are present, and *Wolbachia* based technologies may work only in areas with a single vector species (Walker and Moreira, 2011). In addition, it should be noted that pathogen interference works for newly transinfected species only; attenuation and replacement may pose a significant problem for this technology. Different recent studies have shown that the most important goal for the *Wolbachia* based biocontrol approach to mosquito-borne-disease control is to transfer *Wolbachia* into anopheline mosquitoes, the most-common vectors of human malaria.

Conflict of interest

The authors declare that they have no conflicts of interest.

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