HUMAN FASCOLIASIS: EPIDEMIOLOGICAL PATTERNS IN HUMAN ENDEMIC AREAS OF SOUTH AMERICA, AFRICA AND ASIA

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Abstract. Fascioliasis is an old disease found in prehistoric human populations of the Stone Age, the Mesolithic and the Neolithic periods, and caused by *Fasciola hepatica*, present in Europe, Africa, Asia, the Americas and Oceania, and *F. gigantica*, mainly distributed in Africa and Asia. Considered a secondary disease until the mid-90s, recent research has furnished numerous hitherto-unknown aspects and new information which have given rise to a complete new general picture of this disease, explaining why human fascioliasis has recently been included within the list of important human parasitic diseases by WHO. Liver fluke development is very dependent of the environmental characteristcs according to the nature of free living life cycle phases, which take place fully in the external freshwater milieu, and the vector phase, which develops completely within a freshwater lymnaeid snail, in its turn also very dependent from the environment. Despite of these restrictions, fascioliasis has become the vector-borne disease presenting the widest latitudinal, longitudinal and altitudinal distribution known. Throughout its large geographical distribution, fascioliasis is a well-known veterinary problem. Moreover, studies carried out in recent years have shown it to be an important public health problem as well, human cases having been increasing in 51 countries of the five continents. However, a global analysis of the geographical distribution of human cases shows that the expected correlation between animal and human fascioliasis only appears at a basic level. High prevalences in humans do not seem to be necessarily related to areas where fascioliasis is a great veterinary problem. Three types of human endemic situations in areas presenting human fascioliasis have been established: hypoendemic, mesoendemic, and hyperendemic. The epidemiological classification also includes situations of imported cases and authochthonous, isolated, non-constant cases, as well as epidemic situations, with epidemics in animal endemic areas and epidemics in human hypo-, meso- and hyperendemic areas. Surveys in human endemic areas have proved that, although more prevalent and intense in children, adult subjects are also infected. The gender effect in fascioliasis is worth mentioning, prevalences and/or intensities in human hyperendemic areas appearing to be significantly higher in females. Several human hypo- to hyperendemic areas present a very wide spectrum of epidemiological characteristics related to the very wide diversity of environments. According to the results obtained in the research activities carried out in the different human endemic areas of Europe, the Americas, Africa and Asia, it may be concluded that (i) fascioliasis shows a great adaptation power to new environmental conditions which is the consequence of its own capacities together with the adaptation and colonization abilities of the lymnaeid snail hosts, (ii) well known epidemiological patterns of fascioliasis may not always explain the transmission characteristics in a given area, (iii) when dealing with an endemic zone not previously studied, known epidemiological patterns of fascioliasis must always be taken into account merely as the starting base, (iv) control measures must consider the results of the ecoepidemiological studies undertaken in the zone concerned, as adaptation to new environmental conditions may change transmission characteristics.

INTRODUCTION

Fascioliasis is an important disease caused by two digenetic trematode species: *Fasciola hepatica* in Europe, Africa, Asia, the Americas and Oceania, and *F. gigantica* in Africa and Asia and with less important endemic areas in the southern parts of Europe, Turkey, the Near East, some southern states of the old USSR, particularly Armenia, and only sporadically mentioned in North America. *Fasciola hepatica* is believed to be of European origin, with *Galba truncatula* as the original intermediate host species. In Europe it has been even found in prehistoric human populations of the Stone Age, living at the end of the Mesolithic period, 5000-5100 years ago and the Neolithic (Bouchet, 1997; Aspöck *et al*, 1999; Dittmar and Teegen, 2003), a period marked by the domestication of animals and the development of agriculture, among other characteristics.

Human fascioliasis was considered a secondary disease until the mid-90s. This old disease has a great expansion power thanks to the large colonization capacities of its causal agents and vector species, and is at present emerging or re-emerging in many countries, including both prevalence and intensity increases and geographical expansion. WHO (PVC,

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CPE, Headquarters Geneva) decided to launch a worldwide initiative against human fascioliasis including two main axes: A) transmission and epidemiology studies; B) control activities by mainly treatments with triclabendazole (Egaten®), a single-dose highly effective drug. Results obtained in the research activities included in this WHO initiative during the last years have furnished numerous hitherto-unknown aspects and new information which have given rise to a complete new general picture of this disease, explaining why human fascioliasis has recently been included within the list of important human parasitic diseases by WHO.

THE DISEASE

Fasciolids are parasites of the large biliary passages and the gallbladder. The adult stage has a broad flat, leaf-shaped body, larger in *F. gigantica* than in *F. hepatica*. Morphometric characteristics of both adults and eggs have been shown to vary according to definitive host species (Valero *et al*, 2001a) and also to the geographical origin and altitude (Valero *et al*, 2001b).

Disease is chiefly confined to the liver, so that the most important pathogenic sequelae are hepatic lesions and fibrosis, and chronic inflammation of the bile ducts (Chen and Mott, 1990; Mas-Coma and Bargues, 1997; Mas-Coma *et al*, 1999b, 2000). No association with biliary carcinoma has been reported. Immature flukes may deviate during migration, enter other organs and cause ectopic fasciolosis. In man, the most frequent ectopic lesions are those of the gastrointestinal tract. Other ectopic locations reported are: subcutaneous tissue; heart, blood vessels, the lung and pleural cavity; brain; orbit; abdominal wall; appendix; pancreas; spleen; inguinal nodes; cervical node; skeletal muscle; and epididymis. The usual pathological effects of ectopic lesions are due to the migratory tracks causing tissue damage with inflammation and fibrosis. Parasites may be calcified or become incorporated in a granuloma (Mas-Coma *et al*, 1999b).

The following clinical periods can be distinguished (Chen and Mott, 1990; Mas-Coma and Bargues, 1997; Mas-Coma *et al*, 1999b, 2000):

- incubation phase (from the ingestion of metacercariae to the appearance of the first symptoms): not yet been accurately determined: only "a few" days, 6 weeks, 2-3 months, or even more;

- invasive or acute phase (fluke migration up to the bile ducts): the symptomatology is due mainly to the mechanical destruction of the liver tissue and of the abdominal peritoneum by the migrating larvae causing localised or generalised toxic and allergic reactions lasting 2-4 months; the major symptoms of this phase are fever, abdominal pain, gastrointestinal disturbances, urticaria, and respiratory symptoms; the usual signs are hepatomegaly and splenomegaly, ascites, anaemia, chest signs and jaundice. In human endemic areas, the infection is usually repetitive and the acute lesions are superimposed on chronic disease. Thus, the acute phase may be prolonged and overlap on to a latent or an obstructive phase, fascioliasis chronicity and superimposed repetitive infections posing additional pathological complications (Valero *et al*, 2003);

- latent phase (maturation of the parasites and starting of oviposition): it can last for months or years; the proportion of asymptomatic subjects in this phase is unknown; an unexplained, prominent eosinophilia may already be suggestive of infection; during this phase, infected persons may have gastrointestinal complaints or one or more relapses of the acute symptoms;

- obstructive or chronic phase: this phase may develop after months to years of infection; adult flukes in the bile ducts cause inflammation and hyperplasia of the epithelium; thickening and dilatation of the ducts and the gall bladder walls ensue; the resulting cholangitis and cholecystitis, combined with the large body of the flukes, are sufficient to cause mechanical obstruction of the biliary duct; the proportion of human subjects whose infection develops into the obstructive phase or their prognosis has not been defined; the clinical manifestations in this phase include biliary colic, epigastric pain, fatty food intolerance, nausea, jaundice, pruritus, and right upper-quadrant abdominal tenderness, among others; hepatic enlargement may be associated with an enlarged spleen or ascites; if obstruction is present, the gall bladder is usually enlarged and oedematous with thickening of the wall. Lithiasis of the bile duct or the gall bladder is frequent; the bile duct and the gall bladder may contain blood mixed with bile (haemobilia), blood clots and fibrinous plugs (Chen and Mott, 1990; Mas-Coma and Bargues, 1997; Mas-Coma *et al*, 1999a, 2000).

The associations of fascioliasis with infections by other pathogens appear to be very important from the pathological point of view. The clinic synergistic capacity of fasciolids in coinfection with other pathogenic agents is well known, immunological responses to pathogen antigens being markedly suppressed and concomitant infection being exacerbated following fascioliasis infection (Brady *et* *al*, 1999). The parasitological spectrum of protozoan and helminthic species found in the inhabitants of the human fascioliasis endemic areas, the multiparasitisms, and the associations between liver fluke infection and infection by other pathogenous parasites, all appear to be similar in the different human endemic zones (Esteban *et al*, 1997a, b, 1999, 2002, 2003).

LIFE CYCLE CHARACTERISTICS

The life cycle of both fasciolids comprises four phases, all of which markedly influenceable by the characteristics of the environment and/or human activities (Mas-Coma and Bargues, 1997; Mas-Coma *et al*, 2003):

A) the definitive host harbours the fluke adult stage in the large biliary passages and gallbladder, eggs reaching the external milieu by way of bile and intestine; the definitive host is infected by ingestion of metacercariae; metacercariae excyst in the small intestine within an hour after ingestion, penetrate the host's intestine wall, and appear in the abdominal cavity by about 2 hours after ingestion; most reach the liver within 6 days after excystment; in the liver they migrate for 5 to 6 weeks, preferentially feeding directly on liver tissue; they eventually penetrate into the bile ducts where they become sexually mature; the prepatent period (from the ingestion of metacercariae to the first appearance of eggs in the faeces) is about 2 months (6-13 weeks) in sheep and cattle, varies according to the host, and also depends on the number of the adult flukes in the liver, so that the greater the fluke number, the longer the time to mature and to initiate egg laying; in man, a period of at least 3-4 months is necessary for the flukes to attain sexual maturity; several studies show that the life-span of the parasite in sheep can be as long as 11 years and 9-12 months in cattle; different estimations suggest a life span of the adult fluke in man of between 9 and 13.5 years;

B) the transit between definitive mammal host and intermediate snail host includes the long resistance phase of the egg and the short active phase of miracidium; eggs shed with the mammal faeces will only continue their development if they reach fresh-water of appropriate physico-chemical characteristics; if the climatic conditions are suitable (15-25°C), the miracidia develop and hatch in about 9 to 21 days; if conditions are unfavourable, they may not mature but may remain viable for several months; the miracidium hatchs under light stimulation and swims rapidly until it contacts an appropriate aquatic or amphibious snail host; the miracidium is positively phototropic and negatively geotropic;

C) the development at intermediate host level includes miracidium penetration into the snail, sporocyst, redial generations, production of cercariae and shedding of the latter into water; up to four redial generations have been found, although 3 generations are usually produced after a monomiracidial infection; the redial generations follow the same developmental pattern in different lymnaeid species; cercariae develop within 6-7 weeks at 20-25°C; at lower temperatures the development is delayed; the prepatent period is dependent on temperature, higher temperatures reducing the period (15°C: 56-86 days; 20°C: 48-51 days; 25°C: 38 days);

D) the transit between intermediate snail host and definitive mammal host includes the short swimming phase of cercaria and the long resistance phase of metacercaria until its ingestion by the definitive host; the shedding process takes place between 9° and 26° C, independently of light or darkness; cercariae swim for a short time (1 hour) until contacting a solid support, mostly leaves of water plants above or below the water line; they then lose their tails and quickly encyst, changing into metacercariae; metacercarial cysts become infective within 24 hours after encystment.

DISTRIBUTION OF HUMAN FASCIOLIASIS

Liver fluke development is very dependent of the environmental characteristcs according to the nature of phases B and D, which take place fully in the external freshwater milieu, and phase C, which develops completely within a freshwater snail, in its turn also very dependent from the environment. Despite of these restrictions, *F. hepatica* has succeeded in expanding from the European original geographical area up to actually colonise the five continents. At present, fascioliasis is the vector-borne disease presenting the widest latitudinal, longitudinal and altitudinal distribution known (Mas-Coma *et al*, 2003).

Throughout its large geographical distribution, fascioliasis is a well-known veterinary problem. Moreover, studies carried out in recent years have shown it to be an important public health problem as well (Chen and Mott, 1990; WHO, 1995; Mas-Coma *et al*, 1999a, b). Human cases have been increasing in 51 countries of the five continents (Esteban *et al*, 1998; Mas-Coma *et al*., 1999a, b). Estimations on human infection reach up to 2,4 million (Rim *et al*, 1994), 17 million people (Hopkins, 1992) or even higher depending from the hitherto unknown situations in many countries, mainly of Asia and Africa.

An exhaustive review compiled a total of 7071 human cases reported from 51 countries in all continents in the last 25-year period: Europe, 2951; America, 3267; Asia, 354; Africa, 487; Oceania, 12 (Esteban *et al*, 1998). The real number of human cases is undoubtedly much greater than that published. The major health problems are known in Andean countries (Bolivia, Peru, Chile, Ecuador), the Caribbean area (Cuba), northern Africa (Egypt), and western Europe (Portugal, France and Spain) (Esteban *et al*, 1998). Interestingly, high prevalences in humans do not seem to be necessarily related to high prevalences in livestock, the expected correlation between animal and human fascioliasis only appearing at a basic level.

HUMAN FASCIOLIASIS IN ASIA

Among the published cases from Asian countries reviewed by Esteban *et al* (1998) concerning the previous last 25-year period, most (244) were from Iran, followed by China (41). Less cases were found from Turkey (25), Korea (15), Japan (13), Thailand (6), India (3), Yemen (3), Israel (2) and Saudi Arabia (2). Undoubtedly, those numbers are far away from the reality.

Today we know that in given Asian regions human fascioliasis is an important human health problem, as in the Near East countries surrounding the Caspian Sea. Iran, with epidemics affecting up to 10,000 subjects in Gilan province, in the zone around Rasht and Bandar-e Anzali (Talaie *et al*, 2003) but also with cases in Mazandaran and Isfahan provinces, is the country from which the present knowledge on human fascioliasis is larger. Neighbouring countries as Azerbaidjan, Georgia, Turkmenistan, Tadzikistan, Uzbekistan, or Afghanistan, among others, may almost surely have more or less public health problems related to fascioliasis. Sadykov (1988), in post-mortem examinations, detected fascioliasis in 81 inhabitants of the Samarkand region; *F. hepatica* was in 45, *F. gigantica* in 25, and both species in 11; deaths were apparently not due to fascioliasis, but the findings suggest that fascioliasis is much more frequent than reported.

The lack of knowledge is evident on large Asian regions, as southern Asian Russia, Mongolia, innland China, or Pakistan, India and Bangladesh. Himalayan highlands may also be appropriate for fascioliasis transmission, according to the liver fluke capacity to colonise high altitudes as seen in Andean countries (Mas-Coma *et al*, 2001). The presence of fasciolisis in the Koshi hills of Nepal is well known (Morel and Mahato, 1987).

In eastern Asia, whereas cases in Japan and Korea appear to be sporadic, the situation may be different in the southeastern peninsula. Although few cases have been diagnosed in Thailand from the northern part of the country (Tesana *et al*, 1989), recent information on Vietnam becomes bothering. Only occasional cases of human fascioliasis were reported in Vietnam until the 1990s, but over 500 human cases have been diagnosed between 1997 and 2000 (De *et al*, 2003). The majority of the infected subjects were from central and southern provinces, especially from the coastal and central highland areas (Hien *et al*, 2001b; Cong *et al*, 2001; Xuan *et al*, 2001). The emergence of fascioliasis in Vietnam is an enigma (De *et al*, 2003). Hien *et al*. (2001a) consider the sudden emergence of a large number of human cases between 1997 and 2000 a puzzle and raise many multidisciplinary questions. As stated by De *et al* (2003), this apparent emergence of fascioliasis in Vietnam warrants investigation to find the causes.

EPIDEMIOLOGY

Epidemiological classification of human fascioliasis situations

An epidemiological classification of human infection situations have been recently proposed (Mas-Coma *et al*, 1999a). It includes three types of human endemic situations:

A) Hypoendemic: prevalence less than 1%; arithmetic mean intensity less than 50 epg; high epg numbers only in sporadic cases; human participation in transmission through egg shedding may be neglected; hygiene-sanitation characteristics usually including latrines and waste or sewage disposal facilities; outdoor defecation is not commonly practiced;

B) Mesoendemic: prevalence between 1 and 10%; 5-15 year-old children may present higher prevalences (holoendemic); arithmetic mean intensity in human communities usually between 50 and 300 epg; individual high epg numbers can be found, although intensities over 1,000 epg are rare; human subjects may participate in transmission through egg shedding; hygiene-sanitation characteristics may or may not include latrines and waste or sewage disposal facilities; outdoor defecation may be practiced;

C) Hyperendemic: prevalence more than 10%; 5-15 year-old children usually present higher prevalences (holoendemic); arithmetic mean intensity in human communities usually more than 300 epg; individual very high epg numbers are encountered, intensities over 1,000 epg being relatively frequent; human subjects significantly participate in transmission through egg shedding; hygiene-sanitation characteristics not including the use of latrines; no proper waste or sewage disposal facilities; indiscriminate defecation is commonly practiced.

Two different types of outbreaks according to the endemic/non-endemic situation of the zone can be distinguished:

a) Epidemics in non-human endemic but animal endemic areas: outbreaks appearing in zones where previous human reports have always been isolated and sporadic; such outbreaks usually concern a very few subjects infected from the same contamination source (family or small group reports; contaminated wild, home-grown or commercially grown watercress or other metacercariae-carrying vegetables);

b) Epidemics in human endemic areas: outbreaks appearing in zones presenting human endemics; a more important number of subjects may be concerned; usually related to previous climatic conditions having favoured both the parasite and the snail life cycles; epidemics can take place in hypoendemic, mesoendemic and hyperendemic areas.

Finally, two other situations may be considered:

i) Imported cases: human cases diagnosed in a zone lacking the parasite, even in animals, who were infected in an area where transmission occurs;

ii) Authochthonous, isolated, non-constant cases: humans acquire the infection in an area where they live and where animal fascioliasis is also present; these human cases appear sporadically, without any constancy.

Epidemiological characteristics of human endemic areas

Among human hyperendemic areas, the highest prevalences and intensities known have been found in the Northern Bolivian Altiplano: prevalences in some communities of up to 72% and 100% in coprological and serological surveys, respectively (Hillyer *et al*, 1992; Mas-Coma *et al*, 1995, 1999c; Bjorland *et al*, 1995; Esteban *et al*, 1997a, b, 1999; O'Neill *et al*, 1998); intensities of up to more than 5000 epg in children (Esteban *et al*, 1997a, b, 1999). The results of the surveys proved that, although more prevalent and intense in children (with a peak in the 9-11 age group), adults of the 21-40 and >40 year-old age groups were also infected, with prevalences reaching up to more than 40% in both groups and arithmetic mean intensities of up to 752 and 616 epg, respectively, in given communities (Esteban *et al*, 1997a, b, 1999). Despite the existence of a decrease of the prevalence from children and young subjects to adult subjects, the results demonstrate that in this high endemic zone adult subjects either maintain the parasites acquired when young or can be newly infected as the consequence of inhabiting a zone of high infection risk (Esteban *et al*., 1999). Such a picture suggests that the majority of adult subjects should be in the chronic phase, acute lesions by repetitive infections being superimposed on chronic disease with relative frequency. Thus, the acute phase may be prolonged and overlap with both the latent and the obstructive phase. Although of a lower level, prevalence and intensity situations found in other Andean and African countries (Peru, Egypt) were similar (Esteban *et al*, 2002, 2003).

Interestingly, prevalences and/or intensities in human hyperendemic areas appear to be significantly higher in females. Females shed pronouncedly and significantly more eggs than males in Andean countries (Esteban *et al*, 1999, 2002), whereas in Egypt the prevalence in females appeared to be statistically significantly higher than in males (Esteban *et al*, 2003). This result contrasts with Andean countries, where prevalences do not differ between both sexes (Esteban *et al*, 1999, 2002). The gender role in Egypt may be probably related to cultural, hygienic and behavioural factors, females being more linked to the washing of dresses and kitchen utensils in large canals where transmitting lymnaeids are present, and to agricultural tasks in irrigated plantations as rice fields, as well as to meal preparation in houses including management of freshwater plants potentially carrying attached metacercariae. In Egypt, many species of vegetables and weeds are eaten raw as salads. At child age, girls may be more in contact with transmission foci, according to data collected showing that girls are out from schools more than boys (Esteban *et al*, 2003).

Environment diversity and epidemiological patterns

Human fascioliasis in hypo- to hyperendemic areas of Central and South America, Europe, Africa and Asia present a very wide spectrum of epidemiological characteristics related to the very wide diversity of environments. Such diversity is emphasised by only mentioning that fascioliasis is unique in being capable to give rise to human hyperendemic areas from below sea level (as in the Gilan province, besides the Caspian Sea, in Iran) up to the very high altitude (as in the Andean altiplanos and valleys of Bolivia, Peru, Ecuador and Venezuela). No other vector-borne disease presents such a wide altitudinal range (Mas-Coma *et al*, 2003).

Recent research has shown that there are human hyperendemic areas presenting different transmission and epidemiological patterns, including mainly (i) a very high altitude one related to only *F. hepatica* transmitted by imported *Galba truncatula* in Andean countries following transmission throughout the year, and (ii) another linked to African and Asian lowlands, with overlapping *F. hepatica* and *F. gigantica* and several *Galba-Fossaria* and *Radix* lymnaeids together with secondary transmitting *Pseudosuccinea* and stagnicolines, and where seasonality is typical (Mas-Coma, 2003). Other epidemiological situations are those of human hypoendemic areas in which large epidemics occur, sometimes involving up to 10,000 people, as in Iran (Talaie *et al*, 2003) or less pronouncedly Cuba; in those epidemic areas, lymnaeid species other than the elsewhere main vector species are involved in the transmission.

Within a human endemic area, the parasite distribution appears irregular, the transmission foci being patchily distributed and linked to the presence of appropriate water collections, and human prevalences in school children appear to be related to the distance to water bodies presenting lymnaeids (Mas-Coma *et al*, 1999c).

Disease spreading

The spreading power of fascioliasis is related to the large capacities of fasciolids to colonise and adapt to new environments, even of extreme characteristics as the inhospitality of the very high altitude. Studies undertaken on the Northern Bolivian Altiplano high altitude endemic area (3,800-4,100 m) showed no phase in which the parasite development appears to be negatively modified for the transmission. However, given aspects showed to favour transmission, such as the longer cercarial shedding period and the higher cercarial production, both aspects related to the greater survival capacity of the infected lymnaeid snails. These differences when compared to lowlands may be interpreted as strategies for the adaptation to high altitude conditions (Mas-Coma *et al*, 2001).

The trematode species *F. hepatica* has succeeded in expanding from the European original geographical area thanks to the exportation of European livestock up to actually colonise the five continents where it has adapted to other autochthonous mammal species as camelids in Africa, Andean camelids in South America, and marsupials in Australia (Mas-Coma *et al*, 2003c). The fast capacity of *F. hepatica* to adapt to new definitive host species is illustrated by the examples of the black rat in Corsica island (Valero *et al*, 1998a, 2002; Mas-Coma *et al*, 2003c), the nutria in France (Menard *et al*, 2001) and the pig in Andean countries (Mas-Coma *et al*, 1997; Valero and Mas-Coma, 2000; Valero *et al*, 2001a,b). In all those cases, the newly acquired hosts have proved to play an important role of reservoir host in fascioliasis transmission, contributing to the expansion of the disease, and must, consequently, be taken into account when applying control measures.

The marked differences in preferred snail transmitting species suggest an old parasite/host relationship of *F. hepatica* with *Galba* / *Fossaria* and *F. gigantica* with *Radix*. This assumption is supported by ribosomal DNA markers (18S gene and ITS-2 spacer), which are able to differentiate between lymnaeids transmitting and those non-transmitting fasciolids, as well as between those transmitting *F. hepatica* and those transmitting *F. gigantica* (Bargues and Mas-Coma, 1997; Bargues *et al*, 1997, 2001). The capacity of other lymnaeid species, as those belonging to taxa other than *Galba* / *Fossaria* and *Radix*, to play the role of intermediate host in given circumstances can be explained by a specificity rule, according to which recent parasite species may conserve the capacity of their ancestors of infecting their ancestral hosts besides recently acquired modern hosts (Bargues *et al*, 2001, 2003c). The different specificity of *F. hepatica* and *F. gigantica* is epidemiologically very important, because of the different ecological requirements of their respective *Galba* / *Fossaria* and *Radix* vector species. The lymnaeids transmitting *F. hepatica* are species showing marked amphibious trends and which use to inhabit small or very small water bodies, as those temporal collections depending from seasonal rain. Lymnaeids responsible for *F. gigantica* transmission are species preferring large and deeper water bodies rich in aquatic vegetation, as those more typical for permanent collections. These different characteristics explain that transmission foci of both fasciolids are usually different and appear separate, even in the same endemic locality, and that fascioliasis by *F. hepatica* is more related to seasonality than fascioliasis by *F. gigantica*. However, exceptions are found in human hyperendemic areas as those related to the very high altitude, where *Galba truncatula* is linked to permanent water bodies owing to the high evapotranspiration rates of the high altitude (Mas-Coma *et al*, 1999c).

The fascioliasis colonisation of new environments and geographical areas has taken place not only involving the adaptation of the parasite to new, authochthonous lymnaeid species, but also thanks to the spreading of original lymnaeid vectors. The European *Galba truncatula* spread into other continents most probably together with commercial exportation of livestock (i.e. in mud attached to feet of sheep and cattle). The expanding potential of *G. truncatula* is also related to its capacity for ecological niche widening, as observed on the low human hypoendemic, Mediterranean island of Corsica (Gil-Benito *et al*., 1991). This large island is very mountainous and its climatic conditions (rainfall, temperature) make it difficult to understand its fascioliasis endemic throughout the island. Studies showed that *G. truncatula* is distributed throughout the insular periphery (coastal zones) as well as in the inner regions of the island, up to 1,500 m altitude. Its habitats on Corsica can be classified into two different types: reservoir habitats (permanent presence and renewal of water) and invasion habitats (only seasonal presence of water). From the ecological point of view, numerous different types of biotopes could be distinguished: from large to small rivers, from natural (rivers; water-filled fields; flooding zones; pasture plains) to artificial man-made habitats (large water reservoirs; irrigation channels; fountains; animal drinking-troughs of different types; road lateral ditches) (Oviedo *et al*, 1992). Several atypical habitats may be understood as an ecological niche widening, as a consequence of the influences of the insularity phenomenon. This fact is in turn related to the extraordinary distribution of the disease on the island.

Another lymnaeid species related to fascioliasis spreading is *Pseudosuccinea columella*. This is a rapidly colonising, more aquatic, more heat-tolerant species, which is considered original from Central America, the Caribbean and southern part of North America, but today present in South America, Europe, Africa, Australia, New Zealand and even Tahiti. In Brazil, for instance, *P. columella* appears to be the only lymnaeid present in many fascioliasis areas. Interestingly, a resistant strain of *P. columella* to liver fluke infection has been very recently detected in Cuba, where fascioliasis is transmitted by both *Fossaria cubensis* and *P. columella* (Gutierrez *et al*, 2003). This finding opens research possibilities to look for the genes responsible for resistance and future application in control strategies.

Environment variation in human endemic areas

A large diversity of situations and environments are found in human fascioliasis endemic areas, including different human endemic/epidemic situations, different human demographies, races, diets, habits, traditions and religions, different domestic and wild mammal reservoir species, different lymnaeid transmitting species, zones in both the Northern and Southern hemispheres, altitudes from -27 m up to 4,200 m, hot and cold weathers, seasonal and yearly constant temperatures, scarce to pronounced annual rainfall, low and high mean annual potential evapotranspiration, and from lack of dry period to lack of wet period through different dryness/humidity rates. Moreover, from the landscape point of view, these areas include from altiplanos to valleys, from islands to mainlands, from natural to artificial irrigations, from lakes to lagoons, from large rivers to small streams, and from permanent to temporal water bodies (Mas-Coma *et al*, 2003).

Climatics and human fascioliasis forecast indices

In fascioliasis, climatic factors are decisive in transmission and are pronouncedly related to human infection risks. The yearly definitive host infection incidence of fascioliasis has been related to air temperature, rainfall and/or potential evapotranspiration. These factors affect the intermediate snail host population dynamics and the parasite population at the level of both the free living larval stages of egg and metacercaria and the intramolluscan parasitic larval stages of sporocyst, rediae and cercariae.

Temperature and rainfall influences determine seasonal fascioliasis incidence in many countries, which may be detected on human infection. Thus, human infection has been more frequently observed in the years with heavy rainfall. Although human infections may occur nearly throughout the year, monthly distribution of the fasciolosis human cases exhibited a seasonal distribution which may vary according to the areas. In Europe human infection takes place in summer and autumn and symptoms appear in winter. A prolonged and wet summer in Europe has often been followed by an outbreak of the disease. In Northern Africa, the number of acute human infections appear to peak in August. Sometimes the seasonality is related to the ingestion of infected plants, so that most human cases occurred during the watercress season, October-April, with a maximum from November to February (Mas-Coma *et al*, 1999b).

The adaptation of lymnaeid snails to permanent water collections makes transmission throughout the year possible, as observed in South European countries (Valero *et al*, 1998b), Mediterranean islands (Oviedo *et al*, 1992) and high altitude areas of Andean countries (Mas-Coma *et al*, 1999c), which explains human infection acquired in all months. Where seasonality occurs, temporary transmission is mainly related to the r-strategy characteristics (Mas-Coma *et al*, 1987) of lymnaeid vector species, able to quikly multiply and colonise temporary water bodies from rainfall and to estivate and hivernate during the non-appropriate periods in which those water collections disappear.

Climatic fascioliasis forecast indices are calculated with different equations which take into account variations in these climatic factors. Several have been successfully applied to animal fascioliasis areas, the Water budget-based system index (Wb-bs index) and the Mt index showing to be the most useful. After appropriate climadiagramme studies, modifications of both to fit the high altitude and low latitude characteristics proved to be also useful in human endemic areas of Andean countries. The modified Wb-bs index values allowed to classify the degree of transmission of human and animal fascioliasis in the Altiplanic zones studied into low, moderate and high risk areas (Fuentes *et al*, 1999).

Remote sensing (RS) and geographic information systems (GIS)

These technologies had already been used for animal fascioliasis. Studies were undertaken to analyse whether a GIS predicting model would be viable and useful in the Northern Bolivian Altiplano human endemic zone, where: the transmission foci are stable, the lymnaeids inhabiting mainly permanent water bodies, which enables parasite transmission throughout the whole year; the parasite distribution is irregular, the transmission foci being patchily distributed and linked to the presence of appropriate water collections; and human prevalences in school children are related to the distance to water bodies presenting lymnaeids (Mas-Coma *et al*, 1999c).

The prediction capacity of the RS map based on NDVI data (normalized difference vegetation index values) extracted from 10-day (dekade) composite images from the 1-km AVHRR, acquired by the National Oceanic and Atmospheric Administration's (NOAA) Television Infrared Observation Satellite (TIROS), appeared to be higher than that from forecast indices based only on climatic data. A total overlapping between real ranges of human fascioliasis prevalence and predicted ranges of fascioliasis prevalence (transmission risk through NDVI) is worth mentioning (Fuentes *et al*, 2001).

Climate and landscape change and human fascioliasis

Not only the high adaptation capacities of the liver fluke and the remarkable colonisation potential of their transmitting lymnaeid species play a role in the geographic expansion of fascioliasis. Climate change and man-made modifications of the landscape may also influence pronouncedly (Mas-Coma, 2003b). Climatic anomalies associated with the El Niño-Southern Oscillation phenomenon and resulting in drought and floods are expected to increase in frequency and intensity (Githeko *et al*, 2000). Links to outbreaks of human fascioliasis in the western coast countries of South America, mainly Peru and Ecuador, may be expected.

The colonisation by fasciolids of man-made irrigation systems giving rise to human disease has been recently described in the Puno Altiplano, Peru and the Nile Delta, Egypt (Esteban *et al*, 2002, 2003). In Egypt, human fascioliasis is unexpectedly emerging after many years of successful control measures against schistosomiasis, including both human treatments with praziquantel and molluscicide applications against freshwater snails (Curtale *et al*, 2000).

GENERAL CONCLUSIONS

According to the results obtained in the research activities carried out in the different human endemic areas of Europe, South America, Africa and Asia, it may be concluded that (i) fascioliasis shows a great adaptation power to new environmental conditions which is the consequence of fasciolid capacities together with the adaptation and colonization abilities of the lymnaeid snail hosts, (ii) well known epidemiological patterns of fascioliasis may not always explain the transmission characteristics in a given area, (iii) when dealing with an endemic zone not previously studied, known epidemiological patterns of fascioliasis must always be taken into account merely as the starting base, (iv) control measures must consider the results of the ecoepidemiological studies undertaken in the zone concerned, as adaptation to new environmental conditions may change transmission characteristics.

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