Report of the WHO Informal Meeting on use of triclabendazole in fascioliasis control

WHO headquarters, Geneva, Switzerland
17–18 October 2006
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### Abbreviations

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<tr>
<td>Ab</td>
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<tr>
<td>CL1</td>
<td>cathepsyn L1</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>Fas2</td>
<td>fasciola hepatica cystein proteinase antigen 2</td>
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<td>FBT</td>
<td>foodborne trematodiases</td>
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<td>FES-Ag</td>
<td>fasciola excretory-secretory antigen</td>
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<td>Ig E, Ig G, IgM</td>
<td>immunoglobulins E, G, M</td>
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<td>MoH</td>
<td>Ministry of Health</td>
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<td>NCP</td>
<td>national control programme</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>TCZ</td>
<td>triclabendazole</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Summary

Human fascioliasis is a major public health problem in several areas of the world, including the highlands of Bolivia, Ecuador and Peru, the Nile Delta in Egypt, and central Viet Nam. The infection is global in its distribution; it is estimated that at least 2.4 million people are infected, with more than 180 million at risk of infection. While normally an infection of cattle and sheep, environmental modifications and changes in human behaviour are defining new geographical limits and populations at risk for fascioliasis.

Fascioliasis is caused by the liver flukes *Fasciola hepatica* and *F. gigantica*. Infection occurs when humans consume uncooked aquatic vegetables or drink fresh water contaminated with parasite larvae.

Triclabendazole (TCZ) is the treatment of choice for fascioliasis and is effective at a single dose of 10 mg/kg body weight against the adult parasites in the bile ducts and immature flukes migrating through the liver. TCZ has been used during outbreaks in several countries and for selective treatment of infected individuals in a control programme in the Nile Delta of Egypt. It has not been used in large community-based control programmes because of its limited availability.

Discussions are ongoing to provide a large quantity of TCZ, through the World Health Organization (WHO), for the treatment of human fascioliasis in countries with a high burden of the disease. This will make it possible to scale up treatment at community level. Towards this end, an informal meeting on the use of TCZ in fascioliasis control was convened from 17 to 18 October 2006 at WHO headquarters in Geneva to discuss how such a scale up of fascioliasis control at community level could be implemented, monitored and reported.

The objectives of the meeting were:

1. To determine how TCZ may be used in community-based settings in Bolivia, Egypt, Peru and Viet Nam.
2. To discuss and agree upon a protocol for surveillance of adverse reactions that may arise in community-based use of TCZ.
3. To discuss monitoring the impact of treatment with TCZ on morbidity.
**Introduction**

Foodborne trematodiases (FBTs), including fascioliasis, are neglected in the international public health arena, even in comparison with other helminthic diseases. Even if they cannot be considered as global public health priorities, FBTs are regional and local health priorities for control in several areas of the world. The anthelminthic drugs recommended by the World Health Organization (WHO) as essential drugs to treat these diseases, namely praziquantel and triclabendazole (TCZ), are effective, safe and simple to administer, making treatment on a community-wide basis, and by non-medical staff where necessary, a recommended control option.

WHO recommends the inclusion of FBTs in the group of helminthic diseases whose control relies on the preventive chemotherapy concept, i.e. early administration of anthelminthic drugs, either alone or in combination, to infected individuals to prevent overt morbidity in later stages of life.

The operational implementation of preventive chemotherapy implies the distribution of anthelminthic drugs to the maximum number of people at risk of developing morbidity by making such drugs available at the peripheral levels of the health system, without the need for individual diagnosis. In many resource-poor settings, referral to a proper diagnostic and treatment centre is not a sustainable option; furthermore, in most cases, referral is not necessary as the recommended anthelminthic drugs are safe, with mild and transitory side-effects mainly attributable to killing of parasites and not to the drugs themselves. In this regard, precautions may be necessary during the first rounds of large-scale interventions distributing drugs in areas where helminthic diseases are highly prevalent (due to the high proportion of high-intensity infections). At subsequent rounds, the overall intensity of infections will have been sufficiently reduced to allow for less strict surveillance measures.

The drug distribution strategy may vary according to prevailing epidemiological, logistic and social conditions. Where infected patients adopt early health-seeking behaviour (for example due to early onset of symptomatology) and the health system works properly, treatment should be included in the routine activities of health centres, through an individual case-management approach. In other settings, where prevalence of infection is relatively low and the health system has the capacity to screen a large number of people, active interventions implementing selective treatment of infected individuals may represent the best option. Where health infrastructure is lacking, identification of high-risk groups within populations can allow for systematic, active drug-distribution interventions based on community diagnosis at regular intervals.

In view of the expected availability of a consistent quantity of TCZ, through WHO, large-scale control of fascioliasis should be scaled up in highly endemic areas.

TCZ, the drug of choice against fascioliasis, may well be added to the other anthelminthics currently in the preventive chemotherapy package: the benzimidazoles albendazole and mebendazole, diethylcarbamazine (citrate), ivermectin and praziquantel.
However, there is need to generate information to establish how, under which conditions or with which basic precautions the maximum number of people in need of TCZ treatment can be reached in the safest and simplest possible way, in line with the limited resources available where fascioliasis occurs.

**Global epidemiology of fascioliasis**

Fascioliasis is caused by trematodes belonging to the genus *Fasciola* (*F. hepatica* and *F. gigantica*). In the past, infection was limited to specific and typical geographical areas (endemiotopes), but is now widespread throughout the world, with human cases being increasingly reported from Europe, the Americas and Oceania (where only *F. hepatica* is transmitted), and from Africa and Asia (where the two species overlap). As a consequence, human fascioliasis should be considered as a zoonosis of major global and regional importance.

Paleoparasitological studies have shown that the introduction of *F. hepatica* and its snail host from Europe into the Americas is relatively recent. Today, fascioliasis due to *F. hepatica* is the vector-borne disease presenting the widest latitudinal, longitudinal and altitudinal distribution known. This fact reflects the marked adaptation capacities of both the parasite and the lymnaeid snail hosts and explains the wide geographical distribution of the disease.

Globally, the estimated number of human infections ranges from 2.4 million to 17 million. The epidemiological pattern of transmission in humans is quite wide, and reflects the adaptation of the parasite to different environments. Such patterns may include:

1. cases imported to areas where neither human nor animal fascioliasis is transmitted;
2. autochthonous, isolated, non-constant cases sporadically infected in areas where animal fascioliasis is present;
3. endemic fascioliasis (hypo-, meso-, hyper-endemic);
4. epidemic fascioliasis: (i) in animal endemic areas and (ii) in human endemic areas.

Fascioliasis is the only FBT infection transmitted through both water and food. The following ways of transmission exist:

1. by ingesting encysted metacercariae attached to aquatic or semi-aquatic plants;
2. by drinking water contaminated with floating metacercariae;
3. by ingesting metacercariae attached to the surface of food or kitchen utensils washed with water contaminated with floating metacercariae.

Patients with fascioliasis are frequently found to be coinfected with several other parasites (both helminths and protozoa). A significant association has been established between fascioliasis and giardiasis (*Giardia intestinalis*) in areas where drinking water contaminated with floating metacercariae is habitual. This suggests a common way of transmission for the two parasites.
Distribution in the population may have different patterns; while in countries such as Bolivia, Peru and Egypt most of the infections are usually found in school-age children, in other countries such as Viet Nam cases are mainly women aged 20–50 years; cases occurring during outbreaks in Cuba are mainly adults.

High prevalence rates in humans are not necessarily found in areas where fascioliasis is a great veterinary problem. However, transmission to humans is frequently attributable to environmental contamination by infected animals. Animals susceptible to be reservoir hosts for *Fasciola* species include:
(1) the main domestic animals: cattle, sheep, pigs, buffaloes and donkeys;
(2) sporadic domestic animals: horses, goats, dromedaries, camels;
(3) sylvatic reservoir hosts (lagomorphs such as hares and rabbits for both *Fasciola* species and rodents for *F. hepatica* only).

Research on fascioliasis is now concentrating on defining methods for identifying areas at risk, investigating risky behaviours and patterns of transmission, and assessing the mortality and morbidity attributable to the infection.

**Epidemiology of fascioliasis in Bolivia**
Although sporadic cases are reported from several areas of the country, the northern Altiplano (altitude: 3800–4200 metres), located in the western part of Bolivia, between Lake Titicaca and the valley of the capital city La Paz, is the region most affected by fascioliasis (due to *F. hepatica* only). Transmission foci are patchily distributed and linked to the presence of rivers and subsoil effluences inhabited by the snail intermediate host (*Lymnaea (Galba) truncatula*). Transmission of infection occurs throughout the year, with no marked seasonality, due to the presence of permanent water bodies and of several ecological factors that allow for moderate temperatures and high humidity despite the altitude. Human infection is linked to the consumption of aquatic or semi-aquatic plants such as *Schoenoplectus californicus* (totora), *Nasturtium officinale* (watercress), *Juncus ebracteatus* and algae of the *Nostoc* genus. Children are the age-group most affected by fascioliasis, with prevalence rates as high as 68.2%, due to their habit of sucking and/or chewing such vegetables. Fascioliasis hepatica in the Altiplano is highly prevalent also in domestic animals: 71.6% in ovines, 27.1% in porcines and 25% in bovines; studies carried out in some foci of transmission have shown that 62% of the eggs disseminated in the environment are attributable to ovines, 37% to humans and 1% to other animal species.

**Epidemiology of fascioliasis in Cuba**
In Cuba, sporadic, isolated cases of fascioliasis hepatica are reported on a regular basis. These cases are mainly attributable to consumption of watercress. However, outbreaks also occurred over the past years throughout the island: in Villa Clara Province, an outbreak involved more than 1000 individuals in 1983, while in La Palma (Pinar del Rio Province), an outbreak attributable to consumption of lettuce involved 82 individuals (51 females and 31 males) in January 1995.
Epidemiology of fascioliasis in Egypt

Both *F. gigantica* and *F. hepatica* are transmitted in Egypt. The former has been present since the times of the pharaohs, while the latter was imported from Europe at the beginning of the 1900s. Until the 1970s, only sporadic cases of human fascioliasis were detected, and the first endemic focus, a village in Abiss area near Alexandria, was identified only in 1978. Since 1990, human cases have been reported from most of the Delta governorates, where the overall prevalence is estimated at 3%.

Fascioliasis occurs mainly in children living in rural settings, but also in people living in urban areas. Anaemia is a frequent finding in infected individuals. Symptomatology is usually mild or even absent in children. High prevalence in humans is not necessarily found in areas where fascioliasis is highly prevalent in animals, and in some areas eggs excreted by infected persons may be sufficient to maintain transmission, especially where the habit of defecating outdoors is widespread.

Transmission is linked to dietary habits: many species of vegetables and weeds are eaten raw as salads. Some of them are not aquatic, but are grown along the banks of the water channels. Irrigation and washing after collection expose them to the cercariae. Ingestion of water contaminated with floating metacercariae is also a common means of transmission. Transmission is continuous throughout the year, with a peak at the end of spring or early summer.

Epidemiology of fascioliasis in the Islamic Republic of Iran

The first human case was diagnosed in 1955. Since then, as many as 100 cases per year have been reported from many provinces throughout the Islamic Republic of Iran, mainly Gilan and Mazandaran provinces in the north (around the Caspian Sea), and Isfahan in the central part of the country. In Gilan, where rainfall and population density are high, two major human outbreaks occurred in 1988–1989 and in the late 1990s, each involving thousands of people, mainly in the cities of Bandar-Anzali and Rasht. During such occasions, the Islamic Republic of Iran was the first country to use triclabendazole in humans.

In the Caspian lowland areas, fascioliasis due to *F. gigantica* is highly prevalent especially in cattle, while in rural mountainous areas, animal fascioliasis (due to *F. hepatica*) is less prevalent and mainly involves sheep and goats as reservoirs. However, both fasciolid species frequently overlap in the country, and several different lymnaeid species are intermediate hosts.

Throughout the entire Caspian area, human cases of fascioliasis – mainly from urban settings – are recurrently diagnosed, but the overall prevalence is estimated to be less than 1%. Transmission to humans appears to be linked to consumption of green aquatic vegetables, mainly lettuce and khali-vash (a local variety of watercress). The peak of transmission is from February to June.
Epidemiology of fascioliasis in Peru

The most important foci of transmission of fascioliasis (due to *F. hepatica* only) in Peru are the Cajamarca valley (altitude: 2670 metres), the Huertas-Julcan (altitude: 3420 metres) areas in the Mantaro valley (northern-central Peru) and the Asillo highland irrigation area (altitude: 3909 metres) in Puno Region (southern Peru). Surveys conducted in these areas found prevalence rates of 24%, 21.1% and 25.7% respectively (as detected by Kato-Katz stool examination).

Prevalence of infection is usually highest among children of both sexes; however, women also constitute an important risk group.

The main transmission route may vary in different areas and is linked to local habits: while in the Huertan-Julcan area the consumption of local hot herbal drinks is one of the main risk factors, in the Asillo irrigation area, where the Quechua population do not eat aquatic plants, the main transmission route is probably by drinking-water contaminated with floating metacercariae. In Asillo, coinfection with other helminths or protozoa (especially *G. intestinalis*) is frequent, and high transmission rates are fostered by absence of piped potable water, sewage and rubbish disposal. Indiscriminate defecation is a common practice, and people and animals (sheep, cattle, llamas, pigs and horses) share the same faeces-contaminated water sources.

While the mountainous areas mentioned above are the most affected, cases are also increasingly being reported from Peruvian urban settings.

Epidemiology of fascioliasis in Viet Nam

Before 1997, human fascioliasis (probably due to *F. gigantica*, although the presence of *F. hepatica* in Viet Nam cannot be excluded yet) was only sporadically reported. In the late 1990s, a sudden increase in the number of cases reported made fascioliasis an emerging disease in the country. Since the donation of 1000 tablets of TCZ (Egaten®) in 2004, and 10 000 tablets in early 2006, a further increase in the number of cases has been observed (2000 in the first eight months of 2006), showing that availability of the drugs is likely to produce an increase in cases reported. However, such numbers are still considered a fraction of the actual number of cases occurring throughout the country; underreporting may be attributed to the limited amount of TCZ tablets (still insufficient to meet the country’s needs), and to the fact that TCZ is currently made available to only 10 Vietnamese hospitals, which may prevent poor people from remote areas from seeking treatment.

A situation analysis conducted in the summer of 2006 has shown that the most affected group is women aged 17–49 years. Cases are reported from many districts throughout Viet Nam, but especially from the central part of the country. It is not clear why few cases are reported from the Mekong delta area in southern Viet Nam. Community-based surveys would be needed to obtain a clearer picture of distribution and to fully assess the burden due to fascioliasis.
Further research would also assess whether *F. hepatica* is actually absent from the country; stool examination for eggs is not a routine procedure in Viet Nam, and this may not allow a clear diagnostic distinction between the two forms of fascioliasis.

**Clinical aspects, pathology and pathogenesis**

After an incubation phase, human fascioliasis can be grossly distinguished in acute fascioliasis (when immature worms are migrating through the liver) and chronic-latent fascioliasis (when mature worms are lodged in the bile ducts). In more detail, the following six phases can be identified:

- **Incubation phase**, from ingestion of metacercariae to appearance of first symptoms: this phase can last from a few days to a few months.
- **Acute or invasive phase**: parasites migrate through the liver parenchyma and digest hepatic tissue, causing intense haemorrhage and inflammation that are proportionate to the number of worms; migration tracks can be observed in histological sections; flukes sometimes die, leaving cavities filled with necrotic debris that are eventually replaced by scar tissue. Symptoms (fever, abdominal pain, gastrointestinal disturbances, skin rashes, respiratory symptoms) can last 2–4 months; hepatosplenomegaly, ascites, anaemia, chest signs and jaundice may also be present. Subcapsular haematoma and acute intra-abdominal haemorrhage may complicate the clinical picture. Pyopneumothorax may also occur, following tissue colliquation after larval migration. Immature flukes may deviate during migration, entering other organs and causing ectopic fascioliasis. Symptoms usually disappear when worms reach bile ducts. High leukocyte count especially due to high eosinophilia, and high IgE levels are common features.
- **Latent phase**: the parasites mature and start laying eggs; this phase can last for months or years; symptoms are nonspecific and usually include vague gastrointestinal disturbances; intermittent obstructive episodes with frank symptomatology are possible (see below); signs may include intermittent eosinophilia. Worms that reach the bile ducts may remain there for years. In such cases, fibrosis, hyperplasia and thickening of the walls of the ducts and gallbladder are common findings. The proportion of asymptomatic subjects is apparently high.
- **Chronic (obstructive) phase**: while obstructive episodes may occur intermittently during the latent phase, the chronic phase is characterized by regular and constant obstruction. Parasites, parasite fragments or debris obstruct the common bile duct resulting in swelling of the gallbladder; acute pancreatitis is a possible complication. Obstruction may not resolve within days and lead to jaundice and cholestatic hepatitis. Also, bacterial superinfection with acute cholangitis and cholecystitis may complicate biliary stasis. Symptoms include biliary colic pain (due to obstruction, spasm and distension of the common bile duct), epigastric pain, fatty food intolerance, nausea, intermittent jaundice, pruritus, right upper-quadrant abdominal tenderness and fever (in bacterial superinfection). The frequent occurrence of anaemia is mainly attributable to loss of blood in the bile (haemobilia) due to mechanical damage of the mucosa of the biliary tract, and possibly to increased destruction and decreased production of red blood cells.
• **Advanced chronic phase:** cholecysto- and choledocho-lithiasis and bacterobilia (presence of bacteria in the bile, mainly *Escherichia coli*, *Enterococcus faecalis* and *Klebsiella pneumoniae*) are typical findings, as well as chronicization of cholangitis and cholecystitis. Old worms stop laying eggs.

• **Postinfection phase:** this phase is characterized by clinical sequelae and complications, such as biliary cirrhosis and growth performance deficiencies; worms may act as nuclei for biliary calculi (gallstones), leading to chronic recurrent gallbladder obstruction and eventually to a dilated, atonic gallbladder. Differently from other liver fluke infections, such as clonorchiasis and opisthorchiasis, an association between fascioliasis and cholangiocarcinoma has not been demonstrated so far. In the postinfection phase, most flukes are no longer present in the liver.

Immature flukes may deviate during migration, entering organs other than the liver and causing ectopic fascioliasis. Such worms do not usually achieve sexual maturity and die leaving calcifications or granulomas in the tissues. Ectopic sites include: the gastrointestinal tract (the most frequent), subcutaneous tissue, heart, blood vessels, lung and pleural cavity, brain, orbit, abdominal wall, dorsal spine, appendix, pancreas, spleen, lymph nodes (especially inguinal and cervical ones), skeletal muscles, epididymis, uterus, ovaries and breasts.

Apart from adult worms, both Fas2 (a cysteine proteinase of adult *F. hepatica*) and the parasite eggs trapped in the liver are also likely to play a role in causing calcifications, granulomas and cirrhosis, thus contributing to morbidity. Multiparasitism (concurrent infection with other helminths or protozoa) should also be considered a synergistic determinant of morbidity.

In highly endemic areas, reinfection is common, and new infections may superimpose on old ones; as such, the acute phase may be prolonged and overlap with the latent or chronic ones. The lifespan of the adult worm in humans is between 9 and 13.5 years. Overall, mortality attributable to fascioliasis in humans is low.

**Diagnosis**

Classical coprology (stool examination by the Kato-Katz technique) and serology (using enzyme-linked immunosorbent assay, ELISA) are the most used diagnostic tests in community settings.

The Kato-Katz technique is a quantitative method for detection of parasite eggs in stool samples; it is simple, rapid and inexpensive, making it an option suitable for field conditions and large-scale studies. It is a specific but not sensitive diagnostic test, and has been shown to underestimate by 30% the prevalence obtained by Fas2-ELISA. As a consequence, more than one stool examination might be needed for a proper diagnostic conclusion. The Kato-Katz technique is also unable to diagnose infection in the incubation phase and in the acute phase, meaning that infections within 3–4 months after exposure are easily missed; in addition, it also misses all cases of ectopic fascioliasis.
Immunological tests also exist that allow diagnosis of fascioliasis by detecting specific antigens in stool samples, such as FES-Ag (Fasciola excretory-secretory antigens).

Serological tests, such as Fas2-ELISA or CL1-ELISA, are able to detect the circulating IgG antibodies elicited by infected individuals against these antigens (Fas2 and CL1) secreted by juvenile and adult worms. ELISA allows diagnosis of infection in the incubation and acute phases, and in ectopic fascioliasis as well. In particular, Fas2-ELISA is a highly sensitive (95%) and specific (100%) test.

Despite the use of ELISA in the field, tests performed on stool samples, although less sensitive than those on serum, might be more appropriate for screening communities.

Notwithstanding the availability of such good diagnostic tests, diagnosis of fascioliasis is still a debated subject due to the nonspecific, elusive nature of the clinical picture and the lack of a standardized diagnostic protocol that takes into account the history of the patient, the clinical presentation and one or more tests.

In the acute phase, diagnosis may rely on:
(1) history of ingestion of suspect plants or water usually 2–4 weeks before onset of symptomatology;
(2) clinical symptomatology: this is quite variable and may include fever, tender liver, splenomegaly, bronchitis, pleuritis, pyo-pneumothorax, ascites;
(3) eosinophilia;
(4) detection of anti-Fasciola antibodies in serum (e.g. Fas2-ELISA);
(5) detection of Fasciola excretory-secretory antigens (FES-Ag) in serum and stool;
(6) detection of Fasciola DNA in stool by the polymerase chain reaction (PCR) technique;
(7) imaging (ultrasound): hypoechogenic liver foci migrating from day to day, splenomegaly.

The main differential diagnosis in the acute phase is with visceral larva migrans (toxocariasis, i.e. infection with Toxocara canis), whose larvae also burrow through the liver tissue. The detection of T. canis mobile larvae in the eye using an ophthalmoscope (fundus oculi examination) is pathognomonic of visceral larva migrans.

In the chronic-latent phase, diagnosis may rely on:
(1) conic-cup sedimentation technique (allowing examination of larger quantities of stool than the Kato-Katz technique);
(2) detection of anti-Fasciola antibodies (e.g. Fas2-ELISA) in serum (in order to allow a differentiation between active and past infection);
(3) detection of Fasciola excretory-secretory antigens (FES-Ag) in stool;
(4) detection of Fasciola DNA in stool by the PCR technique;
(5) imaging (ultrasound): crescents, sludge, calculi, tender gall bladder, decreased contractility of the gall bladder; however, the sensitivity of this technique is less than 15%.

Differential diagnosis in the chronic-latent phase includes: (i) gallbladder fibrosis due to schistosomiasis mansoni (this is characterized by echogenic wall thickening, impaired contractility, negativity of the ultrasound-guided Murphy’s sign, absence of calculi,
presence of external protrusions with a smooth internal surface, the association with Symmer’s liver fibrosis, and the possible predictive value for development of liver fibrosis); (ii) clonorchiasis/opisthorchiasis (characterized by recurrent bacterial cholangitis and cholangiocarcinoma); (iii) biliary ascariasis (in case of biliary colics and common bile duct enlargement).

The different combinations of positivity and negativity of coprology (Kato-Katz technique for parasite eggs) and serology (Fas2-ELISA for Anti-Fas2 IgG) can be related with the following different stages of progression of the infection:
- Coprology (−) and serology (−): no infection or infection resolved
- Coprology (−) and serology (+): acute or ectopic infection; infection resolved; biliary obstruction; intermittence of egg shedding
- Coprology (+) and serology (+): liver infection
- Coprology (+) and serology (−): chronic liver infection

**Treatment and treatment outcomes**

TCZ, a benzimidazole compound used in veterinary practice since 1983 and in humans since 1989, is the drug of choice against fascioliasis. It is active against adult parasites in the bile ducts and immature flukes migrating through the liver. Cure rates of 79.4–83.0% have been reported with a single 10mg/kg dose, and 92.2–93.9% with two 10mg/kg doses administered 12 hours apart.

TCZ 10 mg/kg body weight single dose is the regimen of choice. In case of treatment failure (see below for criteria), it is common practice to re-administer TCZ 10 mg/kg followed by another equal dose 12–24 hours apart, for a total dose equivalent to 20 mg/kg.

Adverse reactions to triclabendazole are usually mild. The most common are abdominal pain, epigastric pain and sweating. Less common are nausea, vomiting, dizziness, cough, fever, urticaria and pruritus. Skin rash is uncommon.

Bithionol has long been the drug of choice for fascioliasis. The usual regimen was 30–50 mg/kg per day, divided into 3 oral doses on alternate days for 20–30 days; shorter regimens were also used. Bithionol is no longer recommended due to its prolonged treatment course with moderate to low cure rates and frequent adverse reactions including diarrhoea, anorexia, nausea, vomiting, pruritus, urticaria and abdominal pain; hepatotoxicity was a rarer complication.

Emetine derivatives were also widely used in the past (emetine 1–10mg/kg per day for 10 days; dehydroemetine 1mg/kg per day for 10–14 days). Despite good cure rates, their use is today restricted by the need for parenteral (intramuscular or subcutaneous) administration and the occurrence of adverse reactions including cardio- and hepatotoxicity.

Other common anthelminthics have been used with scarce results: praziquantel is ineffective against fascioliasis, while albendazole, widely used in animal fascioliasis, is
ineffective against human infections. Metronidazole, nitazoxanide and myrrh have also been used with controversial results. Recent experimental results with artemisinin derivatives, however, are encouraging.

**Criteria for cure in hospital settings**

In the acute phase, criteria of cure include:
(1) temporary exacerbation of the clinical picture followed by improvement;
(2) laboratory examinations: decrease of eosinophils and IgE followed later by a decrease in anti-Fasciola antibodies; disappearance of Fasciola excretory-secretory antigens (FES-Ag) in serum; variations in the outcome of the PCR test have not yet been fully clarified;
(3) imaging: no systematic study has yet been published on sensitivity/specificity. The ultrasound picture has been tentatively described: disappearance of hypoechoic foci migrating through the liver and regression of splenomegaly; however, a spontaneous regression of liver changes due to maturation of the worms has been observed, also without cure. Disappearance of signs of complications (haemorrhages, ascites, pleural effusion) has also been observed after treatment.

In the chronic phase, the three primary criteria of cure must be fulfilled by day 60, namely:
(1) clearance of parasite eggs from stool (on three stool samples by conic-cup sedimentation technique);
(2) negativisation of FES-Ag in stool;
(3) absence of crescents visible by ultrasound.

Additional criteria of cure include:
(4) intercurrent biliary colic accompanied by increase of bile duct dilatation/crescent passage, and transient increase in gamma-glutamyl-transpeptidase (GGT) and alkaline-phosphatase (AP), at day 1–7 post therapy;
(5) decrease of anti-Fasciola antibodies;
(6) disappearance of eosinophilia;
(7) disappearance of IgE.

Conversely, primary criteria of treatment failure (the fulfillment of any of which by day 60 is to be interpreted as treatment failure) include:
(1) detection of ova in stools;
(2) persistence of FES-Ag in stool;
(3) crescents seen at ultrasound examination.

Additional criteria of failure include:
(4) persistence of nausea, pruritus, abdominal pain;
(5) increase of anti-Fasciola-antibodies;
(6) persistence of eosinophilia;
(7) persistence of IgE.
Adverse reactions following treatment in endemic countries

A hospital-based survey conducted in Viet Nam by the National Institute of Malariology, Parasitology and Entomology registered a low prevalence and severity of adverse reactions among 51 individuals older than 10 years (most in the age-group 20–49) diagnosed with acute fascioliasis and treated with TCZ 10mg/kg single dose or 10mg/kg twice 6–8 hours apart (total dose 20 mg/kg). The breakdown follows: liver pain: 9/51 (17.6%); abdominal (other than liver) pain: 8/51 (15.7%); fatigue: 6/51 (11.8%); gnawing: 4/51 (7.8%); skin rash: 3/51 (5.9%); vomiting: 1/51 (2.0%); headache: 1/51 (2.0%); dizziness: 1/51 (2.0%).

Adverse reactions following treatment of patients suffering from mixed acute and chronic fascioliasis with TCZ 20 mg/kg single dose were also monitored after an outbreak in La Palma, Cuba. Overall, 82 patients were administered TCZ. The most common adverse reactions were: biliary colic (48.8%); nausea, anorexia, vomiting (8.5%); pruritus (6.1%); jaundice (3.6%). Intensity of reactions was mild (71.6%), moderate (27%) and severe (1.4%). All patients were 15 years or older, with a mean age of 42 years.

In Egypt, TCZ has been widely used to treat fascioliasis since 1998 without any single report of adverse reactions. With reference to the adverse reactions observed during the La Palma outbreak in Cuba (in 1995), in opposition to what was observed in Egypt, the following points were noted:

1. the different age of patients in Cuba and Egypt (adults in Cuba, school-age children in Egypt);
2. the different epidemiological pattern (endemic in Egypt, epidemic/outbreak in Cuba);
3. the different infection stage at which patients are likely to be treated (chronic in Egypt, mixed acute and chronic in Cuba);
4. the different drug dosage adopted in the two countries (10 mg/kg in Egypt and 20 mg/kg in Cuba);
5. the different worm species involved (both F. hepatica and F. gigantica in Egypt, F. hepatica only in Cuba).

All these elements should be carefully considered when adopting a protocol for treatment of human fascioliasis.

Control: perspective and constraints

In Bolivia, no control activity has been implemented so far. Even if the full identification of endemic areas has still to be completed, pilot control exercises may start from the well-known highly-endemic areas of the Altiplano. A proper strategy would be defined following experience learnt from such pilot exercises, and would be discussed with affected communities themselves. The MoH is oriented towards a screening of the population with treatment of positive cases; however, problems may arise with assessment of endemicity through serology because people in endemic areas are reportedly unwilling to give blood samples. Bolivia is experiencing a reform entailing decentralization of health services, and the relevant local health authorities should be fully involved to maximize the chances of success. TCZ is not yet registered for human use in Bolivia.
In Cuba, suspect cases of human fascioliasis are usually reported to hospitals for diagnosis and treatment. Veterinary public health measures and destruction of watercress plantations were carried out in the past and are considered responsible for the overall low number of cases occurring in the country. TCZ is not registered for human use but it has been widely used in research treatment protocols.

Egypt is the only country that is currently implementing control activities against human fascioliasis. Activities started in 1996 with the identification of the six endemic districts in Beheira Governorate. Since then, school surveys have been conducted in all the Delta governorates (8) and in some Upper Egypt governorates (3); a clear picture of the distribution of the infection is now available; age and gender distribution have also been assessed and results published in peer-reviewed literature.

TCZ was registered for human use in Egypt in 1998, the same year that control activities were launched. The strategy is based on school-based, selective treatment. Key activities are regular screening of villages in endemic districts at intervals of around two years and treatment of positive cases: in each village, 100 school-age children are screened using the Kato-Katz technique. If no cases are found, no action is taken; if fewer than three cases are detected, the village is scheduled to be screened again after two years; if more than three cases are detected, all school-age children living in the village are screened and those found positive are treated with TCZ. Screening is made necessary by the fact that most infections in children go unnoticed due to scarce or absent symptomatology.

Control activities are conducted through schools, which are used as treatment points to reach all school-age children, including drop-outs and children not attending school. Only a small amount of treatments are currently carried out through the government hospitals (mainly on adults spontaneously reporting with overt symptomatology).

From 1998 to 2002, the Ministry of Health’s (MoHs) national control programme (NCP) screened almost 36,000 children, and detected and treated 1280 cases of human fascioliasis. Such a selective treatment strategy has proven to be well adapted to the Delta area, where prevalence rates of human fascioliasis are low; it also allowed for identification and treatment of other helminth infections (S. mansoni, A. lumbricoides, T. trichiura, H. heterophyes, T. saginata, H. nana and H. diminuta).

The cost per child treated of such a strategy was calculated to be lower than the amount estimated in case of implementation of a strategy based on administration of treatment to all school-children without prior individual diagnostic screening. Control activities directed against urinary and intestinal schistosomiasis, also prevalent in the Delta area, are carried out by the same team responsible for the control of fascioliasis.

The impact of the NCP on human fascioliasis has been substantial, with a decrease in prevalence of infection from 6% in 1996 to 1% in 2003. Decreases in intensity of infection were also registered from the baseline onwards. In this regard, a treatment interval of two or more years is deemed adequate to maintain low prevalence. No adverse reactions were observed in treated children.
The Egyptian Ministry of Health and Population is confident that the approach implemented in Egypt was successful in limiting the spread of the disease at an affordable cost.

In the Islamic Republic of Iran, control activities are based on health education and individual screening, with treatment of positive cases. Such activities are mainly focused on the highly endemic areas around the Caspian sea. Most cases of human fascioliasis are currently reported from urban settings. TCZ is not registered for human use in the country; however, a waiver from the MoH allows its use for treatment of fascioliasis. The Islamic Republic of Iran has received in-kind donations of TCZ from Novartis Pharma ASG through WHO.

Peru has a well defined methodology for assessing the prevalence of disease in suspect communities, based on combined coprology and serology techniques. The most endemic areas and age-group at highest risk (children) have been identified. The pattern of distribution of the disease within the affected areas is not completely known yet. No control activities have been carried out so far, and a national control strategy has not been defined, yet the MoH is oriented towards an approach similar to that of Egypt, with individual screening of school-age children and treatment of positive cases. Treatment without pre-emptive diagnosis is not considered an appropriate approach because of the focalization of the disease. In highly endemic areas, however, targeted treatment of school-age children without individual diagnosis, or targeted treatment of the entire familial cluster of an infected child, may be an option. In Peru, TCZ should also be made available in urban areas where cases are increasingly reported from. The establishment of an NCP within the MoH would also be a major step forward; however, Peru is undergoing a process of regionalization and therefore the relevant regional authorities should also be involved and empowered. TCZ is not registered for human use in Peru; registration is considered a mandatory step before implementation of large-scale control activities.

In Viet Nam, the situation analysis carried out in August–September 2006 has shown: that the association between pain in the abdominal region and acute fascioliasis is very high and is the cause of early health-seeking behaviour; that a high proportion of infected individuals are egg-negatives at Kato-Katz stool examination; that the diagnostic pathway recommended by the MoHs clinical guidelines (released in August 2006) requires complex examinations and is adapted to provincial and national-level hospitals only; that treatment of fascioliasis entails high hospitalization costs for the patient; that TCZ is not registered in the country for human use.

Based on such findings, the Vietnamese MoH has developed a strategy for control of fascioliasis based on two main points: (i) the decentralization of treatment to district hospitals; and (ii) the adoption of a simplified, more inclusive case definition. The key steps to implement such strategy would be: (a) a wider availability of TCZ; (b) an improved diagnostic capacity at peripheral level; and (c) an increased population awareness of the disease and its prevention through an IEC (information-education-
communication) campaign. The aim of the strategy would be to ensure early treatment of all suspected cases at district hospitals; control based on passive case reporting is justified by the early health-seeking behaviour, and by the expected low prevalence and wide geographical distribution of fascioliasis, which makes active campaigns targeting large sectors of the population inappropriate. The reduction of costs of referral and hospitalization would also be among the expected outcomes of such a strategy. While the complex diagnostic pathway recommended by the MoH guidelines would still be used in national and provincial hospitals, district hospitals would adopt a simplified case definition, making use of diagnostic facilities available at such level; as far as concerns commune health stations, ad hoc training should ensure that all suspected patients are referred to the relevant district hospital.

It is expected that 60 000 tablets of TCZ per year will be sufficient to meet the increased need generated by the adoption of such a more inclusive case-definition adopted at district level; US$ 50 000 would be sufficient to start control activities on a nationwide scale.

Facility for the supply of triclabendazole

Novartis Pharma AG has so far donated TCZ to a small set of countries upon their official request through WHO. Both Novartis and WHO would now wish to move from a case-by-case, country-wise approach to one covering all countries where fascioliasis is endemic in a concerted effort. To this end, Novartis and WHO have agreed to a memorandum of understanding that ensures the supply of TCZ (Egaten®) for three years. A supply of 600 000 tablets would allow for the treatment of 250 000–300 000 people in highly endemic countries, and for control of outbreaks occurring in other countries throughout the world.

To this effect, a logistic structure will be put in place by WHO to ensure the proper delivery of TCZ to countries in need.

WHO will manage the application procedure, and will accept requests only for drugs made by the government of the recipient country. The best way to apply would be for the government to send the application form by e-mail to WHO/headquarters in Geneva, copied to the relevant WHO country office and regional office.

Shipment of drugs will be financially covered by WHO. The addressee will be the MoH of the recipient country. The delivery through the relevant WHO country office can be requested to facilitate customs clearance.
Recommendations

(1) Endemic countries willing to scale up control of human fascioliasis should develop a proper national strategy. Such a strategy should be tailored to the epidemiological characteristics of fascioliasis in that country.

(2) Endemic countries willing to scale up control of human fascioliasis should implement standard surveillance measures to detect possible adverse reactions occurring after large-scale distribution of TCZ. Such measures should be carried out as the monitoring and evaluation component of the pilot phase of the treatment intervention.

(3) Ministries of health of endemic countries willing to access TCZ donated by Novartis Pharma AG to WHO should make an official request to WHO, specifying population to be targeted, number of tablets requested and calendar of treatment. Drugs will be sent with the condition that their use must be accounted for to WHO, and adverse reactions must be reported to WHO.
Annex 1

Surveillance of adverse reactions

The expected availability of TCZ (Egaten®) for public health use will result in an intensified effort to control human fascioliasis. Scaling up of control may entail a shift from individual case management to community-level treatment.

To this end, it is essential to generate data on tolerability of TCZ in a community setting, since one of the likely constraints to scaling up control is the possible occurrence of adverse reactions in heavily infected individuals that may require close monitoring by health personnel. Data on tolerability will also favour a constant supply of TCZ and will allow for a definition or a fine-tuning of an appropriate control strategy for countries where fascioliasis is endemic.

A protocol for surveillance of adverse reactions was discussed and agreed during the Informal Meeting. This protocol aims at elucidating and quantifying the adverse reactions that may follow treatment for human fascioliasis in the context of large-scale public health control programmes. The protocol will include a minimum set of data that need to be collected in each country; additional information can be collected according to the needs and context of the different countries. Surveillance activities in each country should be modelled on the agreed protocol and included as a monitoring and evaluation component of pilot treatment exercises expected to take place in different countries. It is therefore recommended that the protocol be adapted to control activities recommended by the national strategies for control of fascioliasis. WHO would assist with some of the cost of the implementation of such monitoring and evaluation activities.
Monitoring treatment of human fascioliasis with triclabendazole (Egaten®)

Goal
• To assess the extent to which occurrence of adverse reactions following administration of TCZ can limit scaling up of treatment activities in communities highly endemic for human fascioliasis.

Objective(s)
• To ascertain and quantify adverse reactions that may occur following treatment of human fascioliasis with TCZ.
• To analyse the data on adverse reactions experienced by people followed up to help formulate and/or revise guidelines for the use of TCZ in fascioliasis control programmes.

Outcome
• Determination of the nature of surveillance and pharmacovigilance measures that need to be routinely put in place to monitor adverse reactions due to treatment with TCZ in a public health context.

Study type: observational

Study design: active follow-up of a cohort of individuals infected with fascioliasis and treated with TCZ (active cohort monitoring for a defined period of time).

Eligibility: age ≥5 years, both males and females.

Inclusion criteria
• Person infected with fascioliasis
• Willingness and ability to comply with the protocol for follow-up.

Exclusion criteria
• Acute or severe illness, either ongoing or during the previous week
• Chronic severe liver disease
• Pregnant or lactating
• Significant concomitant illness that would interfere with participation or assessment in this study
• Currently on treatment for another illness.
Methodology of follow-up

- **Baseline** (before any treatment activity, in a community where prevalence of human fascioliasis is known)
  - Participants: their name, age and sex are recorded on their personal form. The form is kept by the people conducting the surveys. A treatment card bearing their name, sex and age is given to the participating individual to make recognition at follow-up easy.
  - Participants are interviewed using a structured questionnaire on the occurrence of symptoms that could be confounded with adverse reactions.
  - Participants are asked to provide a stool sample in order to ascertain their status (non-infected, infected, intensity of infection).

- **Day 0** (treatment)
  - Participating individuals infected with fascioliasis are weighed and the appropriate dose of TCZ (10 mg/kg) is calculated and reported on their personal form and on the treatment card.
  - TCZ is administered, (ideally) with a fatty meal or milk, on presentation of the treatment card.

- **Day 1** (24 hours after administration of TCZ)
  - Participating individuals are interviewed on the occurrence of new symptoms since treatment (1st follow-up).

- **Day 4** (96 hours after administration of TCZ)
  - **NB**: follow-up at day 4 OPTIONAL.
  - Participating individuals are interviewed on the occurrence of new symptoms since treatment (2nd follow-up).

- **Day 7** (1 week after administration of TCZ)
  - Participating individuals are interviewed on the occurrence of new symptoms after the last interview (2nd follow-up – 3rd if participating individuals have been followed-up at day 4).
## Criteria and details/options

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details/options</th>
</tr>
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<tbody>
<tr>
<td>Identification data</td>
<td>Name</td>
</tr>
<tr>
<td></td>
<td>Age</td>
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<tr>
<td></td>
<td>Sex</td>
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<td></td>
<td>Height</td>
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<tr>
<td></td>
<td>Weight</td>
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<tr>
<td></td>
<td>Drinking surface water</td>
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<td></td>
<td>Eating aquatic or semi-aquatic vegetables</td>
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<td></td>
<td>Washing dishes</td>
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<td></td>
<td>Access to safe water</td>
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<td></td>
<td>Latrine use</td>
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<td></td>
<td>Keeping animals in the household</td>
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<tr>
<td></td>
<td>Keeping animals with fascioliasis</td>
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<tr>
<td></td>
<td>Kitchen garden</td>
</tr>
<tr>
<td>Personal history</td>
<td>Biliary colic (pain in the right upper abdominal quadrant)</td>
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<td></td>
<td>Other abdominal pain</td>
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<td></td>
<td>Vomiting</td>
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<td>Diarrhoea</td>
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<td>Fever</td>
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<td>Skin rash</td>
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<td>Jaundice</td>
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<td></td>
<td>Fatigue</td>
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<tr>
<td>Symptoms currently being experienced, or experienced in the previous week</td>
<td>Previous cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Significant concomitant illness that would interfere with participation or assessment in this study</td>
<td>Previous cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Examinations</td>
<td>Stool</td>
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<td></td>
<td>Kato-Katz</td>
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<td></td>
<td>Cup sedimentation</td>
</tr>
<tr>
<td></td>
<td>SAF (sodium acetate-acetic acid-formalin)</td>
</tr>
<tr>
<td></td>
<td>Egg genotyping? Y/N</td>
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<td></td>
<td>Haemoccult? Y/N</td>
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<td></td>
<td>FES-Ag? Y/N</td>
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<tr>
<td></td>
<td>Hb</td>
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<tr>
<td>Blood</td>
<td>Leukocyte/eosinophilia</td>
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<td>ALT (GPT)</td>
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<td></td>
<td>AP</td>
</tr>
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<td></td>
<td>Bilirubine</td>
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<td>Serology</td>
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<td></td>
<td>FES</td>
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<tr>
<td>Imaging</td>
<td>Ultrasound</td>
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<tr>
<td>Physical examination</td>
<td></td>
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<tr>
<td>Follow-up (safety assessment)</td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>Day 4 (optional)</td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
</tr>
</tbody>
</table>
Annex 2

Participants form

Name: 
Surname: 
Sex: 
Age: 

Personal identification number: 

Signature:
1. Confounding symptoms

Are you currently suffering from any of the following symptoms, or have you experienced any of them over the past seven days?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Biliary colic (pain in the right upper abdominal quadrant)</td>
<td></td>
</tr>
<tr>
<td>Other abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
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<tr>
<td>Diarrhoea</td>
<td></td>
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<tr>
<td>Fever</td>
<td></td>
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<tr>
<td>Skin rash</td>
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<tr>
<td>Jaundice</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

2. Personal history

Do you …?

A. Drink surface water?
B. Eat aquatic or semi-aquatic vegetables?
C. Wash dishes with surface water?
D. Use latrines?
E. Defecate out in the open?
F. Keep domestic animals (cattle, buffaloes, goats) inside the household?
   a. If yes: as far as you know, are any of these animals affected by fascioliasis?
G. Have a kitchen garden?

Where do you get your water?

☐ tap  ☐ protected well  ☐ unprotected well  ☐ surface water (pond/stream/canal)

3. Parasitology (Kato-Katz)

**FIRST SLIDE (A)**

Eggs found:  YES / NO  Number of eggs/slide:  Number of eggs/gram of faeces:

**SECOND SLIDE (B)**

Eggs found:  YES / NO  Number of eggs/slide:  Number of eggs/gram of faeces:
DAY 0
(TREATMENT DAY)

(DATE: dd / mm / yy)

1. Treatment

WEIGHT:

NUMBER OF TABLETS of EGATEN® 250 mg ADMINISTERED:
DAY 1  
(DAY FOLLOWING TREATMENT)  
(DATE: dd / mm / yy)  

1. 1st follow-up on adverse reactions  
(Patient to be interviewed around 24 hours after treatment)  

Are you currently suffering from any of the following symptoms, or have you experienced any of them since you received treatment?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary colic (pain in the right upper abdominal quadrant)</td>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other abdominal pain</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Severe</td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Skin rash</td>
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<tr>
<td>Jaundice</td>
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<tr>
<td>Fatigue</td>
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<td></td>
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<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
DAY 7  
(ONE WEEK AFTER TREATMENT)  
(DATE: dd / mm / yy)  

1. 2nd follow-up on adverse reactions  
(Patient to be interviewed around one week after treatment)  

Are you currently suffering from any of the following symptoms, or have you experienced any of them since your last interview? 

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
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<tr>
<td>Biliary colic (pain in the right upper abdominal quadrant)</td>
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<td>Other abdominal pain</td>
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<td>Skin rash</td>
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<td>Jaundice</td>
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<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

Additional questions:  

1. Do you feel better now?  
   If YES: which improvement did you experience?  

2. If you were sick again, would you take the treatment again?
Annex 3

Bibliography

Epidemiology


Clinical aspects, pathology and pathogenesis


Diagnosis


**Treatment and treatment outcomes**


**Control: perspective and constraints**

## Annex 4

### Agenda

#### Day 1 – Tuesday, 17 October 2006

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00–0930</td>
<td>♦ Welcome address</td>
<td>Dr D. Engels, Coordinator, NTD</td>
</tr>
<tr>
<td></td>
<td>♦ Introduction of participants</td>
<td></td>
</tr>
<tr>
<td>0930–0945</td>
<td>♦ Meeting objectives and administrative arrangements</td>
<td>Dr L. Chitsulo</td>
</tr>
<tr>
<td>09:45–10:00</td>
<td>♦ Food-borne trematodes, public health relevance and the WHO response.</td>
<td>Dr D. Engels</td>
</tr>
<tr>
<td>10:00–10:15</td>
<td>♦ Epidemiology of <em>Fasciola hepatica</em></td>
<td>Professor S. Mas-Coma</td>
</tr>
<tr>
<td>10:15–10:30</td>
<td>♦ The provision of Egaten®</td>
<td>Dr H. Grueninger</td>
</tr>
<tr>
<td>10:30–11:00</td>
<td>Coffee break</td>
<td></td>
</tr>
<tr>
<td>11:00–11:15</td>
<td>♦ Supply and distribution of triclabendazole</td>
<td>Dr D. Daumerie</td>
</tr>
<tr>
<td>11:15–11:30</td>
<td>♦ Fascioliasis in Bolivia and characteristics of the planned intervention area</td>
<td>Dr R. Angles Riveros</td>
</tr>
<tr>
<td>11:30–11:45</td>
<td>♦ Fascioliasis in Peru and characteristics of the planned intervention area</td>
<td>Dr J. R. Espinoza</td>
</tr>
<tr>
<td>11:45–12:10</td>
<td>♦ Fascioliasis in Viet Nam: epidemiology and control</td>
<td>Dr A. Montresor/ Dr A. Gabrielli</td>
</tr>
<tr>
<td>12:10–12:30</td>
<td>♦ Discussion</td>
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<tr>
<td>12:30–14:00</td>
<td>Lunch</td>
<td></td>
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<tr>
<td>14:00–14:15</td>
<td>♦ Selective treatment for fascioliasis in Egypt</td>
<td>Dr M. M. Youssef</td>
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<td>14:15–14:30</td>
<td>♦ Pathology due to fascioliasis</td>
<td>Dr M. Adela Valero</td>
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<tr>
<td>14:30–14:45</td>
<td>♦ Clinical aspects and treatment of fasciolias</td>
<td>Profesor J. C. Millan</td>
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<tr>
<td>14:45–15:00</td>
<td>♦ Measuring treatment outcomes following specific treatment</td>
<td>Dr J. Richter</td>
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<tr>
<td>15:30–15:30</td>
<td>♦ Discussion</td>
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<td>15:30–16:00</td>
<td>Coffee break</td>
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<tr>
<td>16:00–16:15</td>
<td>♦ Monitoring of adverse events following specific treatment for fascioliasis</td>
<td>Dr A. Gabrielli</td>
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<tr>
<td>16:15–17:15</td>
<td>♦ Discussion on a protocol for pharmacovigilance</td>
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**Closure – 1st day**

#### Day 2 – Wednesday, 18 October 2006

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
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<tr>
<td>08:30–10:30</td>
<td>♦ Discussion on a protocol for pharmacovigilance</td>
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<td>10:30–11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00–12:30</td>
<td>♦ Finalization of protocol for pharmacovigilance</td>
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<td>12:30–14:00</td>
<td>Lunch</td>
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<td>14:00–15:00</td>
<td>Reporting requirements</td>
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<tr>
<td>15:00–15:30</td>
<td>Coffee break</td>
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<tr>
<td>15:30–16:30</td>
<td>♦ Discussion and closure of meeting</td>
<td>Dr D. Engels</td>
</tr>
</tbody>
</table>

**Closure of meeting**
Annex 5

List of participants

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