EPIDEMIOLOGY 1, 2, 3: ORIGINS, OBJECTIVES, ORGANIZATION, AND IMPLEMENTATION

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Abstract. This supplement is a report on the Epidemiology 1, 2, 3(EPI 1, 2, 3) investigation, its origins, evolution, and findings that were carried out over a period beginning in 1990 and ending in 1994 in Egypt. The large scope and size of the study, the largest to date on schistosomiasis in Egypt, was a rationale for publishing a supplement to document EPI 1, 2, 3 methods and results collectively in sufficient detail to serve as a reference for planning, designing, and analyzing future epidemiologic studies and evaluation of schistosomiasis control in Egypt. The 3 objectives of EPI 1, 2, 3 were to 1) determine the changing patterns of Schistosoma haematobium and S. mansoni, 2) investigate factors contributing to differences between villages in the Nile Delta, Middle Egypt, and Upper Egypt, and 3) investigate risk factors for morbidity. The objectives were addressed using standardized techniques, stool and urine examinations, clinical examinations (including abdominal ultrasound), and questionnaires on a selected sample of the populations of selected villages in 9 governorates in Egypt.

Two species of human schistosomiasis are endemic in Egypt, Schistosoma haematobium and S. mansoni. Schistosoma haematobium was discovered in Egypt in 1851 by Theodor Bilharz and the schistosome life cycle was first described in Egypt by Leiper in 1915. In fact, the manifestations of schistosomiasis were described by pharaonic Egyptians in papyri dating from 1500 bc., and calcified schistosome eggs were recovered by Ruffer from 2 Egyptian mummies of the 20th dynasty.

Khalil and Azim in 1937 demonstrated the remarkable impact of converting the ancient form of basin irrigation to perennial irrigation in Upper Egypt on the transmission of S. haematobium. More than two-thirds of Egypt had been converted to perennial irrigation by the 1930s, and by the 1950s most of the arable land in the Egyptian Nile valley had been converted to perennial irrigation including much of old Nubia. El-Zawahry reported that S. haematobium had increased strikingly in those areas of old Nubia where perennial irrigation systems had been constructed.

The Nile Delta, which has always had the largest population of rural Egyptians, had been converted to perennial irrigation before the turn of the century to grow cotton and schistosomiasis endemicity was at a peak when J. Allen Scott conducted his now classic studies on “The Incidence and Distribution of the Human Schistosomes in Egypt” in the 1930s. Scott meticulously described the patterns of S. haematobium and S. mansoni infection throughout the country. He was the first to fully map the disease in Egypt and showed that S. mansoni was restricted to the northern and central parts of the Nile Delta. Schistosoma haematobium was highly prevalent throughout the Nile Delta, where many were infected with both species, and continued to be highly prevalent in Upper Egypt as far south as the Assiut governorate. With some exceptions, Scott found that S. haematobium prevalence decreased to very low levels in the 3 southernmost governorates of Sohag, Qena, and Aswan. These 3 southern governorates had yet to be converted to perennial irrigation, except in isolated areas of sugar cane cultivation.

Following Scott’s work, there was a gap of almost 2 decades before similar data were available. These data, originating from an Egyptian Ministry of Health survey, were reported by Wright. When compared with Scott’s data, as shown in Table 1, changes in the pattern of the 2 species were apparent. Both species had decreased in the Nile Delta, S. mansoni had increased in Giza, indicating future changes, and S. haematobium had decreased in Upper Egypt, except in Sohag, Qena, and Aswan. There were dramatic increases in these 3 governorates where land had been converted to perennial irrigation, details of which are shown in Table 2.

Since that time there have been numerous studies in both Upper Egypt and in the Nile Delta that confirm the trend of decreasing S. haematobium in both of these regions, and a resurgence of S. mansoni throughout the Nile Delta with expansion into Upper Egypt. It is within this context of changing patterns of schistosomiasis endemicity that Epidemiology 1, 2, 3 (EPI 1, 2, 3) was first conceived and is reflected in its 3 objectives; thus, its name. A comprehensive review of schistosomiasis epidemiology in Egypt remains to be published.

ORIGINS AND OBJECTIVES

The Schistosomiasis Research Project (SRP), sponsored by the Egyptian Ministry of Health and the United States Agency for International Development, was designed in 1985 and implemented in 1988. The SRP comprised 6 major research components, one of which was schistosomiasis epidemiology. Within the epidemiology component, there was a number of separate, detailed, research activities. The objective of the first epidemiologic research activity (EPI 1), based upon review of the available data at that time, was to describe the changing patterns of prevalence and incidence of S. haematobium and S. mansoni infection, intensity of infection, and morbidity throughout the endemic areas of Egypt and investigate its causes.

Operationally, EPI 1 was to describe the current pattern of both species and obtain estimates of prevalence and incidence (or related rates) from probability samples representative of populations residing in the cultivated areas of the Nile Valley, including all of the Nile Delta and Middle and Upper Egypt. The Nile Valley, from Aswan north, makes up 8 of the 10 areas (excluding Sinai and Lake Nasser) characterized by the National Schistosomiasis Control Program...
Schistosoma mansoni as endemic for schistosomiasis. Data from EPI 1 would confirm impressions from previous reports and provide a baseline for measuring intensity of infection and rates of infection in addition to prevalence. The measurement of possible risk factors, such as behavioral factors, environmental factors, and chemotherapy programs that might explain patterns or changes, were designed into the study. The mental factors, and chemotherapy programs that might explain patterns or changes, were designed into the study. The epidemiologic factors that could explain village-to-village variation could be measured by ultrasonography has been essentially absent in Egypt. The third objective was to identify factors that explain the differences and new control strategies. Accordingly, the second objective was to identify factors that explain the differences seen in the prevalence of infection, intensity of infection, and incidence between villages and hamlets.

Implementation of this objective required, like EPI 1, probability samples, in this case of large numbers of villages and hamlets (ezbas) so that patterns of infection between villages could be revealed and epidemiologic factors related to these communities and their inhabitants could be investigated.

The third objective (EPI 3) was related to measuring schistosome morbidity. The development of ultrasonography as a clinical tool, the standardization of quantitative ultrasonographic examination methods for measuring schistosome pathology, and the manufacture of portable machines made it possible for the first time to obtain reliable measures of morbidity in Egypt at the community level. The public health impact of schistosomiasis morbidity and specifically the morbidity that could be measured by ultrasonography has been essentially absent in Egypt. The third objective was formulated to address the need for quantitative data on the

### Table 1

<table>
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<tr>
<th>Governorate</th>
<th>Number examined</th>
<th>Number positive</th>
<th>%</th>
<th>Number examined</th>
<th>Number positive</th>
<th>%</th>
<th>Number examined</th>
<th>Number positive</th>
<th>%</th>
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<td>52</td>
<td>12,058</td>
<td>6,131</td>
<td>51</td>
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<td>10,518</td>
<td>5,220</td>
<td>50</td>
<td>1,743</td>
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<td>4,478</td>
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<td>57</td>
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<td>176</td>
<td>4</td>
<td>1,508</td>
<td>4</td>
<td>3</td>
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<td>Aswan</td>
<td>676</td>
<td>91</td>
<td>13</td>
<td>1,029</td>
<td>239</td>
<td>23</td>
<td>676</td>
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<td>Total</td>
<td>27,294</td>
<td>13,138</td>
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<td>70,978</td>
<td>6,430</td>
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* Data were provided by the Ministry of Public Health (MPH) and quoted by Wright.*

### Table 2

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<tr>
<th>Province</th>
<th>District</th>
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<th>Number positive</th>
<th>%</th>
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<td>Abnaub</td>
<td>5,637</td>
<td>704</td>
<td>12</td>
<td>Basin</td>
</tr>
<tr>
<td></td>
<td>Assiut</td>
<td>9,024</td>
<td>2,176</td>
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<tr>
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<td>7,656</td>
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<td>17</td>
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<tr>
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<td>Akhmenn</td>
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<td>Tima</td>
<td>1,892</td>
<td>242</td>
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<td>Qena</td>
<td>Naga Hammadi</td>
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<td>7,218</td>
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<td>1,055</td>
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extent of schistosome morbidity in the endemic areas of Egypt. Moreover, factors that could be identified as morbidity risk factors would also be sought. The third objective was to describe the public health burden of morbidity (determined by ultrasonography) caused by schistosomiasis and identify its determinants in the endemic areas of Egypt.

Again large samples of individuals from both Upper and Lower Egypt were needed. Each participating individual would be examined using standardized ultrasonographic methods on site in the village near the person’s home. Operationally, this objective required the organization of field teams with trained ultrasonographers standardized in the method of ultrasonographic examination. The EPI 3 results were the first to provide national level estimates of schistosomiasis morbidity. Epidemiologic factors or determinants relating to the ultrasonographic findings were investigated. The baseline established by EPI 3 makes it possible for the investigation of prospective changes in ultrasonographic defined morbidity and these investigations are being carried out.

Although each objective constituted a separate investigation, all 3 objectives were complimentary. The logistical and funding advantages of combining the 3 objectives into a single EPI 1, 2, 3 study were obvious. An epidemiologic study design, including sample design, on a national scale that would address EPI 1 objectives was developed that could be used to address the other 2 objectives. Integration of EPI 3, the application of ultrasonography at the village and hamlet level, had the added benefit of enhancing participation by individual villagers selected by the study.

ORGANIZATIONAL AND OPERATIONAL ASPECTS

Before EPI 1, 2, 3 was implemented, the objectives were further specified and made operational. A team of investigators from Egyptian and American institutions were formed. Initially, a sample design of national scope was developed, but it was later modified to fit the availability and location of collaborating Egyptian centers, investigators, and support. Fundamentally, the target population (population universe and domains) was reduced to 9 purposely selected governorates requiring modification of EPI 1 objectives from a national scale sample to the investigation of changing patterns of S. haematobium and S. mansoni infection and intensity of infection independently in each of the 9 selected governorates. The EPI 2 and EPI 3 were modified accordingly. All 9 governorates selected were known to be endemic for either or both species: 4 governorates were selected from the Nile Delta region, 1 from the Suez Canal Zone, and 4 from Middle and Upper Egypt. The Suez Canal Zone, although geographically located in the western Nile Delta, is considered separate from the Delta because it is not irrigated directly by the Nile Delta river branches. The selected governorates are shown in Table 3.

Full probability samples of the rural population for each of these governorates was designed and implemented. The final collective sample size was 120,907 individuals with governorate-specific sample sizes ranging from 7,710 to 18,186.

Investigators and field teams. Each governorate was assigned to 1 of 7 Egyptian investigators located at different collaborating centers. EPI 1, 2, 3 was a multicenter study. Each investigator formed a team that included parasitology technicians and supervisor located at a central laboratory, a data entry-management team, a field team that included an ultrasonographic group headed by a physician, field parasitologist, village census team, interviewers, and an American counterpart. A methodology core team was formed to develop and oversee the integrated study and sample design, write quality control standards for methods and data recording, unify sampling and sample selection across all 9 governorates, and provide the primary site for collective data analysis. The entire EPI 1, 2, 3 was coordinated by the SRP Executive Office.

Several courses were developed specifically for training field team members in the standardization of methods used by the study. A 2-week course was given to all laboratory and field parasitology technicians and their supervisors to standardize the methods for the examination of urine and stool, a 6-week course for standardizing and recording ultrasonographic measures, continued training for field workers responsible for village census and interviewing, and training for data entry and management. Follow-up evaluation of all methods was carried out during the entire study.

Pilot study. In order that all methods were fully tested and unforeseen problems identified beforehand, a full-scale pilot study was conducted in the summer months of 1990. One village was selected by each of the investigators from their respective governorate. A systemic sample of village houses of sufficient number to include 500 or more household members was drawn. Data for all EPI 1, 2, 3 measures were taken, analyzed, and presented at an EPI 1, 2, 3 pilot study conference held in Alexandria later that summer (August 1990). The pilot study experience was invaluable in testing team members on the conduct of the study under village conditions, identifying logistical problems, improving participation rates, revising data forms, questionnaires and census, and sampling methods. Findings from one of the pilot studies has been published.

A more precise description of the epidemiologic and sampling study design, parasitological methods, ultrasonographic methods, quality control methods, and other EPI 1, 2, 3 methods are provided in second paper in this supplement.

Human subjects issues. Participation in EPI 1, 2, 3 and...
in the pilot study as a subject was by invitation and entirely voluntary. In each selected village, individuals living in the selected households, usually the heads of households, were informed about the study and its benefits, told that participation was voluntary, and invited to participate in the study. The invitation was made after obtaining approvals from the Egyptian Ministry of Health, local governorate authorities, and village leaders. Free treatment for schistosomiasis (praziquantel, 40 mg/kg body weight) was provided to all persons found by parasitologic examination of urine and stool to be infected. All results remained confidential. Computer files have records coded only by identification numbers. There were no invasive procedures included at any stage in the study. Stool and urine specimens, an interview, an inspection of the home, a clinical examination, whether or not treatment was accepted, and an ultrasonographic examination comprised exclusively all human data in the project.

Implementation, results, and application. Implementation of the full study in all 9 governorates was initially delayed due to the 1991 Gulf Crisis, which interfered with equipment and transportation procurement. The procurement of vehicles, ultrasonography machines, computers, and laboratory and office equipment and materials necessary for implementation at each participating center or institution was carried out by the Management and Technical Assistance Contractor (MSCI) and in of itself was a major undertaking. The delay provided an opportunity to further pilot test and revise data forms, pretest and modify the quality control programs for parasitology, and debug the computer data entry system installed in each of the centers. When the full study was implemented in 1992, many additional design aspects of the overall study had been improved. Data collection was better standardized and uniform quality control methods were integrated in all participating centers.

The initiation of field work began on receiving the selection of the primary sampling units, villages, and the selection of hamlets and households from core team who drew the list independently for each of the 9 governorates. Each team completed the study in 1 village and then proceeded to the next. After computer entry, the data from each completed village was forwarded to the core team for verification and collective analysis of the overall project. During this period, numerous field visits were made by the investigators, SRP staff, the collaborating investigators from the United States, and core team members to ensure standardization and quality control and solve problems. A complete set of data was made from each of the 9 governorates by the end of 1992.

Preliminary results from all EPI 1, 2, 3 studies were presented at the 1993 International Conference on Schistosomiasis hosted by the SRP in Cairo. Two governorates, Kafr El Sheikh (Nile Delta) and Minya (Middle Upper), have implemented annual follow-up prospective studies. Results from the Kafr El Sheikh study have been published.59–61

Following the report on EPI 1, 2, 3 methodology, there was a separate detailed report on each of the 9 governorates prepared by the respective investigator and his or her team and the respective collaborators from the United States. The data from each governorate were then summarized and collectively assessed and discussed within the context of schistosomiasis epidemiology in Egypt, the NSCP, and possible control options and goals. EPI 1, 2, 3 was designed to be a data-rich project. The descriptive results presented here are only a fraction of the overall material that will continue to be analyzed and reported.

Acknowledgments: Specific acknowledgments have been included in each of the individual reports, which identify individuals that contributed to that respective project. However, EPI 1, 2, 3 was a large undertaking involving many rural Egyptians, field team members, technicians, administrators, and family members for whose participation, assistance, and support we are truly grateful.

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