Establishment of a Binational Cohort to Study *Helicobacter pylori* Infection in Children

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Chronic *Helicobacter* (*H.*) *pylori* infection, typically of childhood onset, causes upper digestive tract diseases of major impact among socioeconomically marginalized populations. This infection is common in children from ethnic minorities in the United States, and particularly so in immigrant children from Mexico. Prevention measures for *H. pylori* infection do not yet exist, given limited understanding of what causes either acute or persistent infection. To address this gap, we initiated the Pasitos Cohort Study to follow children from low-income families in the border region that includes El Paso County, Texas, and Ciudad Juarez, Chihuahua. The children were enrolled prior to birth, and are examined at 6-month intervals to observe the natural history of *H. pylori* infection, and to identify risk factors for acquisition, recurrence, and persistence. This report details the study methods, describes how the cohort was established, and discusses the challenges of compliance with follow up in the border setting. Between April 1998 and October 2000, 1,288 pregnant women were screened for eligibility; 807 of 994 eligible women consented to participate. Birth documentation was obtained for 615 infants, and 472 entered follow up. Successful follow up of this cohort requires resources, including a well-trained, dedicated staff, and incentives, to facilitate and motivate long-term participation. Future findings from this ongoing study will help to fill critical gaps in knowledge regarding the epidemiology of *H. pylori* infection, and will contribute to the identification of prevention strategies. (*Ethn Dis*. 2003;13:387–394)

Key Words: Birth Cohort, Border Health, Child, Cohort Study, Epidemiology, Helicobacter Pylori Infection, Hispanic, Mexico, United States

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Introduction

Chronic *Helicobacter pylori* infection causes upper gastrointestinal diseases of major impact among socioeconomically marginalized populations worldwide.[1] Age-specific prevalence patterns across populations suggest that most *H. pylori* infections are initially acquired in childhood.[2] Although the highest prevalence in children has been noted in developing countries,[2] data from the National Health and Nutrition Examination Survey III (1988–1991) estimated a seroprevalence of 25% in US children aged 6–19 years[3]; in this national sample, the prevalence was 42% in Mexican Americans, 40% in non-Hispanic Blacks, and 17% in non-Hispanic Whites. Among the Mexican Americans, the prevalence in those born outside the United States or Canada was 58%. In addition, elevated seroprevalence was observed in children whose family income was below the poverty line, whose household head had fewer than 12 years of education, and whose homes had a high density of persons per room.

Since its identification in 1983, *H. pylori* is documented to be among the most ubiquitous human bacterial infections, colonizing perhaps half, or more, of the world's population, often without symptomatic manifestations. Early investigations confirmed that *H. pylori* was a cause of acute gastritis,[4] which tends to become chronic if left untreated. In 1994, a National Institutes of Health Consensus Panel concluded that *H. pylori* causes most human peptic ulcers.[5] Also during 1994, an International Association for Research on Cancer working group determined that the evidence linking *H. pylori* infection to cancer of the stomach was sufficient to conclude that *H. pylori* infection is carcinogenic to humans.[6] Chronic gastritis and peptic ulcer disease are relatively common in populations across the globe, while gastric cancer is a major cause of cancer mortality in developing countries, as well as in some immigrant groups in the United States. However, effective public health control measures for this infection have not yet been identified. Important obstacles to prevention and control include limited knowledge of the natural history and determinants of *H. pylori* infection. In particular, little is known about acute *H. pylori* infection, the proportion of acute infections that persist, and the determinants of persistent infection.

What we know so far about the epidemiology of *H. pylori* infection stems largely from seroprevalence studies.[1,2,7] *H. pylori* seroprevalence has been linked consistently to low socioeconomic status and, in particular, to residential crowding.[1,8] The problematic detection of *H. pylori* has presented obstacles, however, to clearly identifying the main portals of entry and exit in the human host, as well as pinpointing or ruling out environmental reservoirs.[1] Though evidence suggests that person-to-person transmission is likely, the relative importance of fecal-oral, oral-oral, and gastric-oral (through vomitus) pathways is unclear; evidence suggestive of waterborne and zoonotic transmission has also been reported.[1,8,9]

Given the well-known limitations of cross-sectional studies,[10] prospective epidemiologic studies are needed to identify modifiable risk factors for persistent

H. pylori infection. Because this infection is acquired most often in early childhood, unresolved questions regarding determinants of infection can be addressed effectively by following a cohort of children from birth, in a setting in which they are likely to become infected in early childhood. The Pasitos Cohort Study (named for the local project name, *Pasitos para la Salud,* or "baby steps for health") follows children from low-income families in the border region that includes El Paso County, Texas, in the United States, and Ciudad Juarez (Juarez), Chihuahua, in Mexico, a region with elevated rates of both gastric cancer and infectious diseases. Cohort children were identified prior to birth, and are examined at 6-month intervals to observe the natural history of *H. pylori* infection, and to identify risk factors for acquisition, recurrence, and persistence. While data addressing the major study goals are not yet available, this report details the study methods, describes how the cohort was established, and discusses the challenges of compliance with follow up in the border setting.

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METHODS

Location

The El Paso/Juarez border region faces myriad public health hazards. Infectious diseases are of particular concern, due to the large number of residents on both sides of the border lacking connections to a potable water supply, and/or adequate excreta disposal facilities. El Paso, with a population of approximately 680,000, is the largest US city on the United States-Mexico border, and its sister city, Juarez, with a population of approximately 1,614,000, is the largest Mexican city on this border; this international port of entry is among the busiest in the world. In this region, substandard living conditions are common on both sides of the border. According to 1997 US Census data, 28% of El Paso residents, and 39% of El Paso children, live below the poverty line, making El Paso one of the poorest metropolitan areas in the United States. A report to the US congress in 1994 estimated that 40,000 residents of El Paso County did not have treated water piped into their homes, and that a larger number did not have adequate excreta disposal. Evidence of the potential impact of *H. pylori* infection in El Paso is an elevated rate of stomach cancer mortality: 9.9/100,000 in El Paso males, compared with 6.6/100,000 for all males in Texas; 5.0/100,000 in El Paso females, compared with 3.0/100,000 for all females in Texas.[11]

The Pasitos Cohort Study draws its population from 3 Hispanic border communities: Socorro, Texas; San Elizario, Texas; and Juarez, Mexico. San Elizario is a poor community bordering Juarez to the east of El Paso, comprising "colonias," defined as rural subdivisions, with limited water and sewage disposal infrastructure. Travel between the United States and Mexico is common for residents of San Elizario, many of whom are recent immigrants with relatives in Mexico. Socorro lies on the border adjacent to San Elizario. In contrast to San Elizario, Socorro residents are more likely to have grown up in the United States, to speak English, and to have higher levels of education. The sanitation infrastructure of Socorro is better than that of San Elizario. Juarez is the fourth largest city in Mexico. Electricity, water, sewage disposal, and natural gas are available for most Juarez residents, but are lacking in areas of poorer housing populated by low-income families. Juarez had no sewage treatment facility until 2000.

Design

Pregnant women were invited to enroll their expected child in a cohort study. The women were recruited at public assistance clinics in El Paso County, and at maternal-child clinics in Juarez. At baseline, interviewers obtained information on family and household characteristics through questionnaires administered in person, and women were screened for *H. pylori* seropositivity. For further indication of the unborn cohort child's potential exposure to *H. pylori* infection from family members after birth, we offered *H. pylori* testing to any of the unborn infant's siblings who were under 6 years of age. Study staff monitored the enrolled pregnant women to obtain birth information, and began examining the cohort children at 6-month intervals, starting at 6 months of age. At the ongoing follow-up visits, the field team tests the cohort children for *H. pylori* infection, measures their height and weight, and interviews the mothers regarding hygiene-related exposures, illnesses, medications, and diet.

Recruitment

Study staff recruited pregnant women using consecutive sampling at recruitment sites. Initially, potential participants were screened for eligibility. Eligibility required an age of 17 years or more, a gestation of 20 weeks or more, and a stated intention to return to the clinic with the infant after birth. Eligible women received an explanation of the study, and were invited to complete informed consent protocols. El Paso County women came from 2 Women,

Infants, and Children (WIC) clinics, administered by the El Paso City-County Health District, one each in Socorro and San Elizario. Juarez participants came from maternal-child clinics of the Mexican Social Security Institute (IMSS). The national IMSS system provides comprehensive health care to private-sector employees and some other groups; it covers 60% of the Juarez population, most of whom are low-income, but not destitute.

Follow Up of Children

Around the expected date of birth, study personnel sought the following information regarding each enrolled infant: date of birth, sex, birth weight, and length. El Paso participants reported this information to WIC personnel when they enrolled the infants for benefits immediately after birth. For Juarez participants, no such central source of birth documentation was available; therefore, Juarez participants were asked to inform study staff of the infant's birth. When the child was nearly 6 months of age, data collectors contacted participants to schedule the initial follow-up exam. The time window for scheduling the visit was from 2 weeks before, through 2 weeks after, the date the child became 6 months of age. These ongoing visits are scheduled at 6-month intervals. To facilitate the mothers' clinic schedules, some visits occur before the target time window; when visits are not completed by the target age, attempts are made to complete the visit as soon as possible thereafter. At each follow-up visit, mothers are interviewed regarding the child's health, water sources for drinking, bathing, and swimming, contact with other children, and diet, as well as changes in the household environment. The child's weight and height are measured, and samples of breath and blood are collected for *H. pylori* testing. When younger siblings are born into families of Pasitos Cohort children, the siblings are invited to participate as well.

Classification of *H. pylori* Status

At baseline, mothers and siblings were tested for *H. pylori* IgG serum antibodies, using a commercial enzyme immunoassay. To classify infection status in the cohort children, we employ 2 methods. In addition to the enzyme immunoassay to detect *H. pylori* IgG serum antibodies, we also use the 13C-urea breath test, which detects urease activity in the stomach as a marker of active *H. pylori* infection.[12,13] For the antibody test, we collect 2 capillary tubes of blood from the children, by heel stick during infancy, and finger prick when the children are older. For the breath test, we collect breath samples from infants using a pediatric mask connected to an aluminum bag by a one-way valve. Older children blow through a tube into the bag. The breath test requires a baseline sample, collected prior to having the child drink juice containing 13C-labeled urea, and another sample collected 20–30 minutes later. The 13C/12C ratio is measured by infrared spectrometry; positivity is based on an elevated isotope ratio in the second breath sample.[14,15] Validation studies of the urea breath test have shown excellent accuracy in children, although questions have been raised about its accuracy in infants and toddlers.[2] Evidence suggests that predetermined cut off values for commercial serological assays, based mainly on validation in adults, may have low sensitivity in children, who tend to have low antibody levels.[2] Given these uncertainties, we are conducting our own studies of test accuracy for this cohort.

Ascertainment of Household Exposures

Cohort mothers were interviewed at the time of enrollment to obtain information on the participants' households prior to the child's birth. This included family demographics, geographic location, mother's residential history, parents' occupation, education level and income, number of rooms and beds in the home, number of indoor bathrooms, source of drinking water, water purification practices, respondent's handwashing habits, type of sewage disposal system, place of health care, and type of health insurance. This information is updated at each follow-up visit.

Ascertainment of the Child's Health Status

At each follow-up visit, interviewers measure the child's height and weight according to the recommended procedures in the Anthropometric Standardization Reference Manual.[16] These anthropometric measures will be used to monitor height-for-age, and weight-for-height, as growth indicators.[17] Hematocrit levels, available from blood collected at each visit, will be used to detect anemia. Mothers report any illnesses and medications the child has had, or taken, in the preceding 6 months, aided by a medicine calendar, on which they are asked to record this information prospectively between visits; they are also asked to keep medication packages to show interviewers, for additional accuracy of the information.

Ascertainment of Diet

At each follow-up visit, mothers report the child's usual dietary intake (frequency of foods consumed and portion sizes) during the previous week in response to an interviewer-administered quantified food frequency questionnaire (FFQ). The FFQ data will allow for analysis of total energy intake and intake of macro- and micronutrients, as well as of food consumption patterns. The FFQ was derived from the 1994–1996 Continuing Survey of Food Intakes of Individuals[18], and was adapted to include the most important food sources in our study population.

Epidemiologic Outcomes

Given that *H. pylori* infection is generally not detected at onset, cases must be detected by screening. Cases in chil-

dren who screen positive after a previous negative follow up can be considered incident. Because evidence suggests that children are not infected prenatally, all children are assumed to have negative *H. pylori* status at birth (though they may have maternal antibodies).[19] For incident cases, the time of onset will be defined as occurring at the midpoint of the interval since the prior follow-up visit. The following infection frequencies will be estimated from the follow up of Pasitos Cohort children: incidence rates (incident cases/person-months without infection); spontaneous clearance rates (recovered cases/person-months with infection); persistence (cumulative duration of infection in months); and recurrence (number of episodes of infection during follow up).

Human Subjects Protection

This study received human subjects protection approval from the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston, the Institutional Review Board of the University of Texas, El Paso, the local and national levels of the Mexican Social Security Institute, and the Office for Protection from Research Risks of the National Institutes of Health.

ESTABLISHMENT OF THE PASITOS COHORT

Recruitment of Mothers

Of 1,309 pregnant women approached for eligibility screening between April 1998 and October 2000, 1,288 (98%) agreed to be screened, and 994 were eligible (Figure 1). Of the eligible women, 807 (81%) agreed to participate, and 801 (402 El Paso, 399 Juarez) completed baseline data protocols prior to the child's birth. Two women who consented to participate, but did not complete the interview at enrollment, brought their children for follow up; one completed the baseline interview later, while the other has not yet returned to provide the missing data.

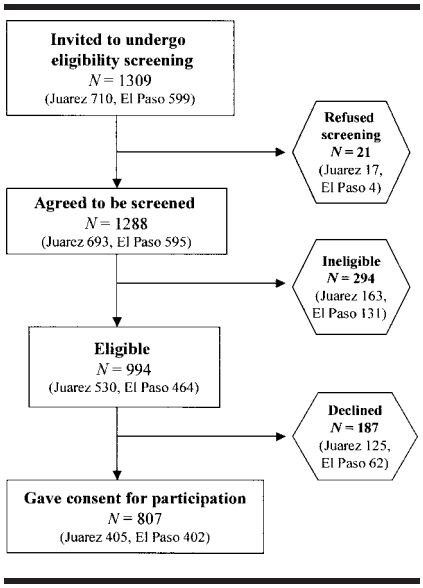

Fig 1. Recruitment of pregnant women for the Pasitos Cohort Study

Study Population Characteristics

Characteristics of the households of women who consented to participate, and who completed interviews at baseline, appear in Table 1. In the El Paso County study site of Socorro, households (*N*=268) have a median of 5 members, and a median crowding index (persons/room) of 0.8; 79% of the Socorro households use municipal tap water for drinking, and 40% have sewer connections. In the El Paso County study site of San Elizario, households (*N*=136) have a median of 5 members, and a median crowding index of 1.0; 66% of San Elizario households use municipal tap water for drinking, and 13% have sewer connections. Participating households in Juarez (*N*=399) have a median of 5 members, and a median crowding index of 1.2; 53% of Juarez households use municipal tap water for drinking, 89% have sewer connections, and 23% have no indoor bathroom.

Establishment of the Pasitos Birth Cohort

Entry into the Pasitos birth cohort occurred when the child completed the first follow-up visit, for which the target age was 6 months. The first of the Pasitos cohort children became 6 months of age and entered follow up in October 1998; the last of the participating children became 6 months of age in August 2001. As of July 1, 2002, 472 children had returned for one or more follow-up visits. Figure 2 shows the age distribution of the children at their first follow-up visit, when they entered the cohort. Sixty-four percent entered follow up at 5.5–7.4 months of age; 15% at 5.5–5.9 months, 20% at 6.0–6.4 months, 20% at 6.5–6.9 months, and 9% from 7.0–7.4 months. Five percent entered before reaching 5.5 months of age; therefore, 60% came in for follow up before 7 months of age. Another 19% entered the cohort at 8–12 months of age, and 98% began follow up by the age of 15 months. The last child entered follow up in June 2002, at 18 months of age. Figure 3 presents the establishment of the birth cohort.

FOLLOW-UP CHALLENGES

This study demands a considerable commitment from participants, given the amount of time and cooperation required from the mothers and their children. On average, screening interviews required 10 minutes, and baseline interviews required an additional 30 minutes. Follow-up visits require 2 data collectors, and take an average of 40 minutes to complete, with one researcher interviewing the mother, while the other collects height and weight measurements, as well as blood and breath samples, and attends to the child and any

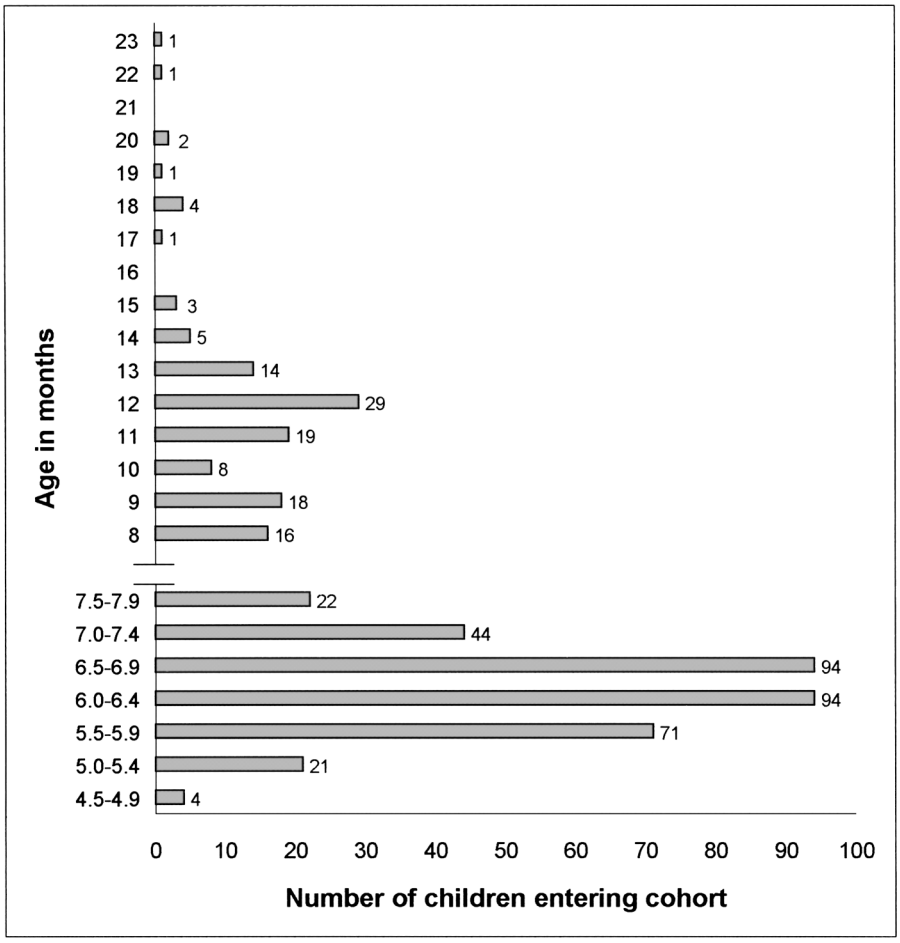

Fig 2. Age at entry into the Pasitos Cohort Study

young siblings so the mother can focus on the interview.

The low-income populations included in this study present some additional challenges for follow up, largely due to lack of stability in the circumstances that permit continued participation. Follow up of Juarez participants is further complicated by their greater geographic dispersion, and the inability to contact most of them by telephone. Juarez participants without telephones are sent telegrams to remind them of follow-up appointments. To improve compliance with follow up, study staff began conducting visits in the homes of El Paso participants. This is facilitated by WIC rules, which require women to attend the clinic closest to their home; as a result, El Paso participants live in a relatively small geographic region. Home visits proved highly successful in improving follow up among El Paso participants. Conducting home visits for Juarez participants has not proved efficient, due to logistic problems.

Efforts to maximize compliance with follow up include maintaining warm relations with participants, determining reasons for reluctance to participate, making repeated attempts to contact participants to schedule follow-up visits, and interacting with children and mothers in ways that minimize discomfort during visits. Cohort members who do not return after birth are kept in active follow up, with repeated contact attempts made until the child would be 18 months of age, or there is a clear indication that the child has withdrawn from participation. Cohort members who appear for the first time after 18 months of age are welcomed into the study. We also offer incentives to further encourage compliance. Mothers responded well to receiving a package of disposable diapers at each follow-up visit, until the children began reaching the age when they were no longer using diapers. At that point, we introduced books and educational toys as alternative incentives, which also proved popular. In addition, after each visit, the child keeps a colorful plastic bottle or training cup (depending on the age) used to administer juice for the breath test. Testing children's hematocrit levels turned out to be an inadvertent incentive for Juarez mothers, who express great concern about anemia in their children.

DISCUSSION

The Pasitos Cohort Study offers a unique opportunity to study determinants of a common infectious disease of childhood, with important consequences for chronic disease in socioeconomically marginalized adult populations. The United States-Mexico border setting of this study, where the sanitation infrastructures of developed and developing countries interface, adds to the uniqueness of this research. Another innovation is the collaboration between United States and Mexican community health agencies, facilitating the examination of a health problem common to populations on both sides of the Rio Grande.

We searched the literature for other studies that used follow-up data to track *H. pylori* status in children over time, and identified 19 such studies. Nine of the reports were based on stored sera from studies originally conducted for

other purposes[20–28]; most of the retrospective studies did not measure infection status at regular follow-up intervals, and some used intervals of several years. Ten studies tracked *H. pylori* infection in children prospectively: 5 tracked antibody levels[29–33]; 4 tracked active infection using the urea breath test[19,34–36]; and one tracked active infection using a stool antigen test.[37] Of the prospective studies, 5 followed children for about one year, and 5 followed children for about 2 years. Among the prospective studies that provided details, the cohort sizes ranged from 48 to 345; the average was 115, with only one study following more than 200 children. Of the 8 prospective studies that provided information on mean follow up, the average was 1.2 years. Seven of the 19 studies examined determinants of *H. pylori* seropositivity in childhood[22,25,26,28,29,32,33]; these studies examined diverse factors in varied age groups and geographic settings, and did not reach consistent conclusions. Only one study that tracked active infection, rather than antibodies, examined any risk factors, and these were limited to antibiotics, although the study did not have adequate statistical power for drawing conclusions.[37] None of the 19 studies attempted to distinguish factors influencing disease acquisition from those determining persistence.

In conclusion, the Pasitos Cohort Study represents a unique effort to investigate a communicable disease that constitutes a major public health burden, and disproportionately affects socially marginalized groups. The cohort comprises a population of low-income United States-Mexico border children, with varied exposures experienced by the 3 socioeconomically distinct communities from which the cohort was drawn. Successful follow up of such a population requires resources, including a well-trained, dedicated staff, and incentives, to facilitate and motivate long-term participation. The socioeconomic diversity of this cohort will facilitate the

Table 1. Study population characteristics

	Juarez		El Paso	
	N	%	*N*	%
Total	399	100	402	100
Number of household members				
2–3	60	15.0	43	10.7
4–5	198	49.6	191	47.5
6–7	90	22.6	124	30.8
8–17	51	12.8	44	10.9
Number of older siblings of cohort infant				
0	112	28.1	143	35.6
1	147	36.8	142	35.3
2	99	24.8	72	17.9
3–6	41	10.3	45	11.2
Father lives in household	357	89.5	233	58.0
Household crowding (persons per room)				
≤1	179	44.9	320	79.6
>1	220	55.1	82	20.4
Rent or own current home				
Own	166	41.6	123	30.6
Rent	112	28.1	82	20.4
Live in someone else's home rent-free	121	30.3	197	49.0
Number of times mother moved in past 5 years				
0	141	35.3	118	29.4
1–2	204	51.1	222	55.2
3+	54	13.5	62	15.4
Mother has health insurance/Medicaid*	113	28.3	286	71.1
Household income†				
Very low	76	19.0	118	29.4
Low	140	35.1	123	30.6
Low-Medium	83	20.8	70	17.4
Medium	61	16.8	32	8.0
Don't known	39	9.8	59	14.7
Type of floor in home				
Dirt	11	2.8	0	0
Cement	239	59.9	35	8.7
Carpet, linoleum, tile, wood	149	37.3	367	91.3
Working refrigerator in home	367	92.0	400	99.5
Currently own a car that runs	229	57.4	373	92.8
Type of cooling system				
Central air	111	27.8	264	65.7
Window AC	147	36.8	111	27.6
Electric fans/none	140	36.1	24	6.0
Other	0	0	3	0.7
Drinking water source				
Municipal piped in house	196	49.1	262	65.2
Municipal piped in patio	17	4.3	1	0.2
Bottled water/vending machine	149	37.3	100	24.9
Public tap/tanker truck/well	9	2.3	5	1.2
Other (combinations of above)	28	7.0	34	8.5
Type of disposal system				
Sewer	355	89.0	123	30.6
Septic tank	16	4.0	261	64.9
Cesspool	28	7.0	7	1.7
Other	0	0	4	1.0
Toilet or latrine				
Latrine	42	10.5	2	0.5
Flush toilet	355	89.0	394	98.3
Other	1	0.3	5	1.2

Table 1. Continued

	Juarez		El Paso	
	N	%	*N*	%
Number of indoor bathrooms				
0	93	23.3	4	1.0
1	288	72.2	233	58.0
2+	18	4.5	165	41.0

* All Juarez participants have full healthcare coverage through the Mexican Social Security Institute; some have private health insurance in addition.

† Very low—Juarez, <$2000 pesos/mo, El Paso, <US $10000/yr; Low—Juarez, $2000-$3999 pesos/mo, El Paso, US $10000–$14999/yr; Low–Medium—Juarez, $4000–$5999 pesos/mo, El Paso, US $15000–$24999/yr; Medium—Juarez, ≥$6000 pesos/mo, El Paso, ≥$25000/yr.

identification of determinants of the acquisition, recurrence, and persistence of *H. pylori* infection early in life. Findings from this study will help to fill critical gaps in knowledge regarding the epidemiology of *H. pylori* infection, and will contribute to the identification of prevention strategies.

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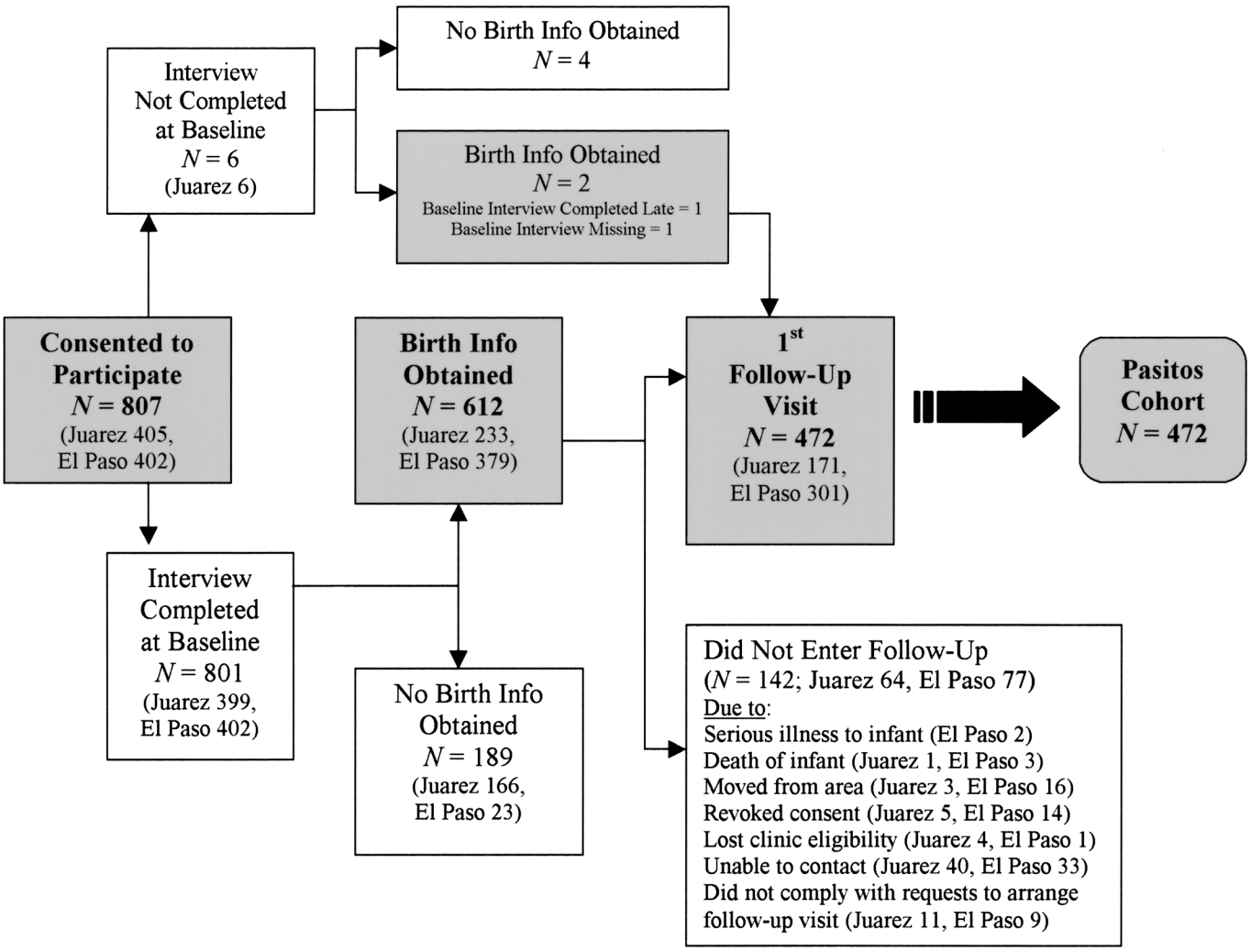

Fig 3. Establishment of the Pasitos birth cohort

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