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Sponsor: Sanofi Pasteur **Drug substance:** CYD Dengue Vaccine	**Study Identifiers:** NCT00788151, 2014-001711-40 **Study code:** CYD24
Title of the study: Immunogenicity and Safety of a Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 11 Years Previously Vaccinated against Yellow Fever in Peru	
Study center: 1 study center in Peru.	
Study period: Date first subject enrolled: 26/Sep/2008 Date last subject completed: 16/Aug/2010	
Phase of development: Phase II	
Objectives: 1) To describe the humoral immune response to dengue before and after each injection with dengue vaccine in 2 age cohorts of children (2 to 5 years and 6 to 11 years) previously vaccinated with YF vaccine. 2) To evaluate the safety of each vaccination with dengue vaccine in 2 age cohorts of children (6 to 11 years and 2 to 5 years) 3) To describe viremia after the first and second vaccinations with dengue vaccine in a subgroup of 130 randomized subjects (100 subjects in Dengue Vaccine Group and 30 subjects in Control Group) in 2 age cohorts of children (6 to 11 years and 2 to 5 years)	
Methodology: Randomized, blind observer, controlled, monocenter, Phase II trial in 300 children in Peru. There were 3 vaccinations (on Day 0 [D0], D0+6 months, and D0+12 months) and 2 groups of subjects as follows: • **Dengue Vaccine Group** received a 5555 formulation (~5 $\log_{10}$ cell culture infectious dose 50% [$CCID_{50}$] of serotypes 1, 2, 3, 4) of sanofi pasteur's CYD dengue vaccine as first, second, and third vaccinations. • **Control Group** received a placebo (sodium chloride [NaCl] containing human serum albumin) as first and second vaccinations, and pneumococcal polysaccharide vaccine (Pneumo23®) as third vaccination.	
Number of subjects: Planned: 300 Randomized: 300 **Evaluated:** Full analysis set: 298 Safety: 298	

Diagnosis and criteria for inclusion:

Inclusion criteria were checked either at Screening (Scr.) only, at Scr. and at the first vaccination visit (Scr. + V01), or at the first vaccination visit only.

1) Aged 2 to 11 years on the day of inclusion (Scr.)
2) Subject in good health, based on medical history, physical examination and laboratory parameters (Scr. + V01)
3) Provision of Assent Form signed by the subject (for subjects ≥ 8 years old) and Informed Consent Form signed by the parents or another legally acceptable representative (and by an independent witness for illiterate parent[s]) (Scr.)
4) Subject and parents/legally acceptable representative able to attend all scheduled visits and to comply with all trial procedures (Scr. + V01)
5) For a female subject of child-bearing potential (girls post-menarche), avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to first vaccination, until at least 4 weeks after the last vaccination (Scr.+V01)
6) Documented receipt of YF vaccine since at least 1 month before the first vaccination (Scr.)

Study treatments

Investigational product: CYD Dengue Vaccine

Form: Powder and solvent for suspension for injection

Composition: Each 0.5 mL dose of reconstituted vaccine contained:

5 ± 1 log10 (CCID50) of each live, attenuated, dengue serotype 1, 2, 3, and 4 virus (5555 formulation)

Excipients: essential amino acids, non-essential amino acids, L-arginin chlorhydrate, saccharose, D-trehalose dihydrate, sorbitol (D), tris (hydroxymethyl) aminomethane, and urea

Solvent: NaCl 0.4% containing human serum albumin 2.5%

Route of administration: Subcutaneous (SC)

Control Product for First and Second Vaccinations: Placebo (NaCl containing human serum albumin, diluent used for CYD dengue vaccine reconstitution)

Form: Liquid

Composition: NaCl 0.4% containing human serum albumin 2.5%

Route of administration: SC

Control Product for Third Vaccination: Pneumo23® (pneumococcal polysaccharide vaccine)

Form: Solution for injection in a pre-filled syringe of 0.5 mL

Composition: Each 0.5 mL dose of vaccine contains:

Purified capsular polysaccharides of Streptococcus pneumoniae (25 µg of each of the following serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F)

Excipients: phenol as preservative ≤1.25 mg; isotonic buffered solution up to 0.5 mL (sodium chloride, disodium phosphate dehydrate, and sodium dihydrogen phosphate dehydrate)

Route of administration: SC

Duration of participation: The expected duration for per subject is 18 months

Criteria for evaluation:

Immunogenicity

- Neutralizing antibody levels against each of the 4 parental dengue virus serotype strains of dengue vaccine were measured in sera collected from all the subjects before and 28 days after each vaccination (dengue neutralization assay)

Safety

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination
- Occurrence, time to onset, number of days of occurrence, intensity, and action taken of solicited (pre-listed in the subject's diary and electronic case report form [eCRF]) injection site reactions occurring up to 7 days after each vaccination
- Occurrence, time to onset, number of days of occurrence, intensity, and action taken of solicited systemic reactions occurring up to 14 days after each vaccination
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each vaccination
- Occurrence of any serious adverse events (SAEs) throughout the trial.
- Occurrence and timing of out-of-normal-range biological test results at 8 and 15 days after the first and the second vaccinations in 130 randomized subjects

Viremia

Occurrence and level of dengue vaccine viruses in sera collected 8 and 15 days after the first and after the second vaccinations in 130 randomized subjects by quantitative reverse transcriptase-polymerase chain reactions (qRT-PCRs).

Statistical methods:

All the main analyses were descriptive. For the main parameters, 95% Confidence Intervals (CIs) of point estimates were calculated using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

Age cohorts were analyzed together (pooled) and separately.

One statistical analysis of safety and immunogenicity was performed on unblinded data after the third vaccination and one final statistical analysis was performed after the 6-month follow-up.

Summary:

Subject Disposition and Demographic Characteristics

Overall, a total of 300 subjects were randomized in this study. Of these 300 subjects, 2 subjects did not receive any vaccine. Of the 298 subjects who received at least one vaccination, 199 subjects were randomized to the Dengue Vaccine Group and 99 subjects to the Control Group.

Of the 298 subjects who received vaccination, 92.6% of subjects completed the study and 7.4% of subjects discontinued the study during the trial. The most common reason for not completing the study was voluntary withdrawal not due to an adverse event (6.4%). The percentage of subjects who withdrew voluntarily was similar in the Dengue Vaccine Group (6.5%) and in the Control Group (6.1%).

The other reasons for discontinuations were: 1 subject (0.3%) was non-compliant with the protocol, 2 subjects (0.7%) reported other adverse event which led to discontinuation (both were from the Control Group and experienced increased transaminases).

Female subjects slightly outnumbered male subjects in the Full Analysis Set, with the proportion of males and females almost equal in the Dengue Vaccine Group (50.8% to 49.2%) but slightly lower in the Control Group (46.5% to 53.5%).

In both treatment groups, the mean age was 6.4 years and the median 5.9 years, with an overall range from 2.0 to 12.0 years (the age of the oldest subject was slightly under 12 based on protocol definition but was rounded up to 12.0).

Demographic characteristics were similar across treatment groups. The mean height was 111.9 cm in the Dengue Vaccine Group and 110.7 cm in the Control Group, while the medians were identical at 109.0 cm. Mean weight was 21.9 kg in the Dengue Vaccine Group and 20.8 kg in the Control Group, while median weights were 18.9 kg and 19.3 kg, respectively. BMI values were almost identical, with means of 16.8 kg/m^2 and 16.5 kg/m^2 for the dengue and Control Groups, respectively, and medians of 16.3 kg/m^2 and 16.2 kg/m^2, respectively.

Safety and Viremia

Safety

There were 6 subjects reporting 7 SAEs: 2 SAEs were reported in the Dengue Vaccine Group and 5 in the Control Group. None of these SAEs were assessed as related to the vaccination by the Investigator or the Sponsor. All the subjects recovered.

There was no subject reporting immediate unsolicited AEs.

Solicited injection site reactions

After the first vaccination**:** The rates of solicited injection site reactions were similar in both the Dengue Vaccine Group and Control Group. The most frequent reaction was pain, reported in 20.6% of subjects in the Dengue Vaccine Group and 17.2% of subjects in the Control Group after placebo vaccination. No injection site reactions in either group were of Grade 3 intensity. The majority of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days of vaccination, and lasted 1 to 3 days. In the Dengue Vaccine Group, 1 subject from the younger cohort experienced Grade 1 erythema for 8 days.

After the second vaccination: The rates of solicited injection site reactions were similar in both the Dengue Vaccine Group and Control Group. Again, the most frequent reaction was pain, seen in 19.7% of subjects in the Dengue Vaccine Group and 17.4% of subjects in the Control Group after placebo vaccination. The majority of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days of vaccination, and lasted 1 to 3 days. In the Control Group, 1 subject reported Grade 3 injection site pain.

After the third vaccination: The rates of solicited injection site reactions were about twice as high in the Control Group after administration of Pneumo 23 vaccine. Pain was reported by 17.7% of subjects in the Dengue Vaccine Group versus 32.2% of subjects in the Control Group. The majority of the solicited injection site reactions were of Grade 1 intensity, appeared within 3 days of vaccination, and lasted 1 to 3 days. In the Dengue Vaccine Group, 1 subject (0.5%) from the younger cohort experienced swelling of Grade 1 intensity for 8 days and 1 subject (0.5%) experienced pain of Grade 3 intensity. In the Control Group, 2 subjects (2.2%) reported Grade 3 pain and 3 subjects (3.3%) each had erythema and swelling of Grade 3 intensity.

Age cohort comparison: In the Control Group only after the third vaccination with the peumo23 vaccination, the rate of solicited injection site reactions was lower in the younger cohort (30.2%) compared to the older cohort (40.4%). In the Dengue Vaccine Group, this rate was similar across age cohorts after any vaccination.

Solicited systemic reactions

After the first vaccination: The rates of solicited systemic reactions were higher in the Dengue Vaccine Group than in the Control Group. The most frequent solicited systemic reactions were headache, malaise, and fever, reported respectively in 35.7%, 33.7%, and 31.3% of subjects in the Dengue Vaccine Group compared to 16.2%, 23.2%, , and 10.1% of subjects in the Control Group. The majority of reactions were of Grade 1 or Grade 2 intensity, appeared within 3 days of vaccination and lasted 1 to 3 days. In the Dengue Vaccine Group, Grade 3 fever was reported by 7 subjects (3.5%) and Grade 3 headache, malaise, and asthenia each by 1 subject (0.5%). The majority of these Grade 3 reactions were associated with concomitant infections. No Grade 3 reactions were reported in the Control Group.

After the second vaccination: The rates of solicited systemic reactions were similar between the treatment groups, and tended to be lower than they had been post–Dose 1 in the Dengue Vaccine Group. The most frequent systemic reaction was headache, reported by 22.3% of subjects in the Dengue Vaccine Group and 19.6% of subjects in the Control Group. In the Dengue Vaccine Group and in the Control Group respectively, Fever was reported by 19.7% and 16.3% of subjects; malaise by 18.1% and 16.3% of subjects; and myalgia by 14.9% and 10.9% of subjects. The majority of the solicited systemic reactions were of Grade 1 or Grade 2 intensity, appeared within 3 days of vaccination and lasted 1 to 3 days. There were few reactions of Grade 3 intensity. In the Dengue Vaccine Group, Grade 3 myalgia was reported by 2 subjects (1.1%), Grade 3 headache, malaise, asthenia and fever were reported each by 1 subject (0.5%). In the Control Group, Grade 3 malaise was reported by 2 subjects (2.2%), and Grade 3 headache and asthenia were reported each by 1 subject (1.1%).

After the third vaccination: All solicited systemic reactions were reported by > 10% of subjects in both groups, and were higher in the Control Group (Pneumo23 vaccine) than in the Dengue Vaccine Group. The most frequent was headache, reported by 18.8% of subjects in the Dengue Vaccine Group and by 27.8% of subjects in the Control Group. In the Dengue Vaccine Group and Control Group respectively, fever was reported by 18.4% and 22.5% of subjects; malaise by 16.7% and 23.3% of subjects; myalgia by 13.4% and 26.7% of subjects; and asthenia by 10.2% and 16.7% of subjects. The majority of the solicited systemic reactions were of Grade 1 intensity, appeared within 3 days of vaccination and the number of days of occurrence was 1 to 3 days. In the Control Group, 1 subject experienced headache with a maximum intensity of Grade 3 that lasted for 15 days. In the Dengue Vaccine Group, no reactions of Grade 3 intensity were reported. In the Control Group, Grade 3 fever was reported by 3 subjects (3.4%); Grade 3 headache was reported by 3 subjects (3.3%); Grade 3 malaise and myalgia were reported by 2 subjects (2.2%); and Grade 3 asthenia by 1 subject (1.1%). The rate of Grade 3 solicited systemic reactions was higher after Pneumo 23 vaccination compared to the dengue vaccine Dose 1.

Age cohort comparison: After any vaccination, the rates of solicited systemic reactions were lower in the younger cohort (71.0%) than in the older cohort (77.8%) in the Dengue Vaccine Group. This rate was similar across age cohorts in the Control Group.

Unsolicited AEs:

After the first vaccination: The rates of unsolicited AEs were similar in both groups. The most frequent unsolicited AEs in all groups were reported in the SOC of infections and infestations. In both treatment groups, the most frequently reported unsolicited AEs were nasopharyngitis and pharyngitis: respectively, 13.6% and 10.6% in the Dengue Vaccine Group and 13.1% and 14.1% in the Control Group. The majority of the unsolicited non-serious AEs were of Grade 1 or 2 intensity, appeared within 15 days of vaccination and lasted less than 14 days. A total of 3 AEs were of Grade 3 intensity. In the Dengue Vaccine Group, 1 subject reported Grade 3 urinary tract infection, and in the Control Group, 1 subject reported Grade 3 transaminases increased (which resolved spontaneously) and Grade 3 headache.

After the second vaccination: The most frequently reported unsolicited AEs were pharyngitis (13.8%) in the Dengue Vaccine Group and nasopharyngitis (14.1%) in the Control Group. The majority of the unsolicited non-serious AEs were of Grade 1 or Grade 2 intensity, appeared within 15 days of vaccination and lasted less than 14 days. In the Dengue Vaccine Group,1 subject from the older cohort reported Grade 3 tonsillitis .

After the third vaccination: The most frequently reported unsolicited AEs in all groups were reported in the SOC of infections and infestations. The most frequently reported unsolicited AE was nasopharyngitis in the Dengue Vaccine Group (4.8%) and in the Control Group (13.3%). The majority of the non-serious unsolicited AEs were of Grade 1 or Grade 2 intensity, appeared within 15 days of vaccination and lasted less than 7 days. In the Dengue Vaccine Group, 1 subject from the younger cohort reported Grade 3 pyrexia.

Age cohort comparison: After any vaccination, the incidence of unsolicited AEs was higher in the younger cohort than in the older cohort in both treatment groups.

Vaccine Viremia on Day 8 and Day 15 after the first and second vaccination:

There was no subject from the Control Group with viremia.

YF RT-PCR method (non-serotype specific vaccine viremia): In the Dengue Vaccine Group, 38.1% (37/97) of subjects had detectable viremia and 1.0% (1/97) of subjects had quantified viremia on Day 8 after the first vaccination. Only 6.3% (6/95) of subjects had detectable viremia and there was no subject with quantified viremia on Day 15 after the first vaccination.

There were 8.8% (8/91) of subjects with detectable viremia and no subject with quantified viremia on Day 8 after the second vaccination. No subject had detectable or quantified viremia on Day 15 after the second vaccination.

Pan flavivirus RT-PCR method (non-serotype specific vaccine viremia): None of the subjects from either group had quantified viremia. In the Dengue Vaccine Group, 8.2% (8/97) of subjects had detectable viremia on Day 8 after the first vaccination and 3.3% (3/91) of subjects on Day 8 after the second vaccination. There were no subjects with detectable viremia on Day 15 after either the first or the second vaccination.

CYD RT-PCR Method (serotype-specific dengue vaccine viremia): The serotype specific dengue vaccine viremia 8 and 15 days after the first and second vaccinations was low in all subjects across the age cohorts and after each vaccination. Among the 37 subjects with positive YF RT-PCR on Day 8 after the first vaccination, no subjects had detectable viremia for serotype 1, 5.4% (2/37) of subjects had detectable viremia and 2.7% (1/37) of subject had quantified viremia for serotype 2, 5.4% (2/37) of subjects had detectable viremia for serotype 3; and 91.9% (34/37) of subjects had detectable viremia and 5.4% (2/37) of subjects had

quantified viremia for serotype 4. Among the 6 subjects with positive YF RT-PCR on Day 15 after the first vaccination, no subjects had detectable viremia for any serotypes. Among the 8 subjects with positive YF RT-PCR on Day 8 after the second vaccination, no subjects had detectable viremia for serotypes 1 and 2, 12.5% (1/8) of subject had detectable viremia for serotype 3 and 75.0% (6/8) of subjects had detectable viremia for serotype 4. The highest percentage of subjects with detectable viremia was for serotype 4.

Biological Abnormalities

The percentage of subjects with biological abnormalities 8 days after the first vaccination was low and similar in the Dengue Vaccine Group (6.2% [6/97]) and the Control Group (6.7% [2/30]). Whereas 15 days after the first vaccination, the percentage of subjects with biological abnormalities was slightly lower in the Dengue Vaccine Group (5.3% [5/95]) as compared to the Control Group (6.9% [2/29]). No clinically significant biological abnormalities were reported in Dengue Vaccine Group; one was reported in a subject in the Control Group (Grade 3 ALT increase). Overall, the percentage of subjects with biological abnormalities was lower after the second vaccination compared to the first vaccination.

After the second vaccination: 2 clinically significant biological abnormalities were reported in the Dengue Vaccine Group (2.2%) (Grade 1 AST and ALT increase); and one clinically significant biological abnormality was reported in the Control Group (3.6%) (Grade 1 AST increase).

Immunogenicity

Two different assays were used for immunogenicity assessment: microneutralization assay at pre and post each vaccination and PRNT at pre and post-Dose 2 and post-Dose 3. Overall, the same trends were observed with both assays, however all results (GMTs values and seropositivity rates) for serotype 2 were higher when measured with the PRNT than when measured with the microneutralization assay.

Dengue Humoral Immune Response (Microneutralization Assay and PRNT)

Seropositivity

Microneutralization assay: In the Control Group, the percentage of subjects who were seropositive for each serotype at baseline ranged from 18.2% for serotype 4, to 38.4% for serotypes 1 and 3. These percentages did not change appreciably following each of the 3 vaccinations. In the Dengue Vaccine Group, the seropositivity rates increased sharply from baseline to 28 days post–Dose 1 for serotype 4 and roughly doubled for the other serotypes; then slightly contracted by the time of the second dose 5 months later, however remained considerably higher than baseline; and increased sharply again at 28 days post–Dose 2 to reach >98% for all serotypes except serotype 2. The rates slightly contracted by the time of the third dose 5 months later, however remained higher than it had been at pre–Dose 2; and at 28 days post–Dose 3, it was restored to post–Dose 2 levels.

PRNT assay: In the Control Group, the percentage of subjects who were seropositive for each serotype at baseline did not change appreciably after the second and the third vaccinations. In the Dengue Vaccine Group, the percentage of subjects who tested positive at baseline ranged from 19.3% for serotype 4 to 35.0% for serotype 3. In this group, by 28 days post–Doses 2 and 3, more than 94.0% of subjects were seropositive for antibodies to all 4 serotypes.

Age cohort comparison: With the microneutralization assay, the seropositivity rates were slightly lower in the younger cohort than in the older cohort while with the PRNT, the seropositivity rates were slightly higher in the younger cohort than in the older cohort.

Overall, the majority of subjects, in this population previously vaccinated with YF, achieved seropositivity after 2 doses of dengue vaccine. The seropositivity rates were greater than 96.0% post-Dose 3 for serotypes 1, 3 and 4 with both assays.

Seropositivity for at Least 1, at least 2, at least 3 or all 4 Dengue Virus Serotypes

Microneutralization assay: In the Control Group, the percentages of subjects who were seropositive at baseline did not change appreciably following any of the 3 vaccinations. In the Dengue Vaccine Group, the percentages of subjects who were seropositive at baseline for at least 1, at least 2, at least 3, or all 4 serotypes were 32.2%, 29.1%, 19.6%, and 10.6%, respectively. These rates more than doubled following the first vaccination to 80.8%, 66.8%, 52.8%, and 37.8%; and after the second vaccination reached 100% for at least 2 serotypes, 98.4% for at least 3 serotypes, and 66.0% for all 4 serotypes. Following the third vaccination, the rate was > 98.0% for at least 3 serotypes and 79.0% for all 4 serotypes.

PRNT assay: In the Control Group, the percentages of subjects who were seropositive at baseline did not change appreciably after the second and the third vaccinations. In the Dengue Vaccine Group, the percentages of subjects who were seropositive at baseline for at least 1, at least 2, at least 3, or all 4 serotypes were 37.6%, 31.5%, 29.9%, and 17.3%, respectively. These rates strongly increased after the second vaccination to 99.5% for at least 2 serotypes, 98.4% for at least 3 serotypes, and 90.9% for all 4 serotypes. Following the third vaccination, the rate was 99.5% for at least 2 serotypes, 98.4% for at least 3 serotypes, and 94.1% for all 4 serotypes.

Age cohort comparison: The results for both the younger cohort and the older cohort were similar.

Overall, more than 98.0% of subjects were seropositive after the third vaccination for at least 3 dengue virus serotypes with both assays. Seropositivity rates for all 4 serotypes slightly lower with the microneutralization assay are the result of the low levels of neutralizing antibodies to serotype 2 with this method.

Dengue Neutralizing Antibody Levels:

Microneutralization assay: For the Control Group, baseline GMTs for each serotype did not appreciably change following each dose, except a slight increase observed for serotype 1 after the third vaccination (23.9 to 35.3 1/dil). For the Dengue Vaccine Group, Baseline GMTs were similar to those of the Control Group, however showed a considerable increase after each dose of dengue vaccine: from baseline to 28 days after the first, second and third dose of dengue vaccine respectively, from 18.8 to 43.1, 214 and 254 1/dil for serotype 1; from 7.55 to 15.5, 21.4 and 22.3 1/dil for serotype 2; from 13.1 to 41.4, 128 and 99.2 1/dil for serotype 3; and from 7.52 to 87.9, 158 and 147 1/dil for serotype 4. The trend was similar for each serotype: i.e. increase from baseline following Dose 1 (with a dominant response for serotype 4); a much higher increase and broad response to the four serotypes following Dose 2; and either a modest increase (serotype 1) or a plateau (serotypes 2, 3 and 4) following Dose 3.

PRNT assay: For the Control Group, baseline GMTs for each serotype did not appreciably changed following each dose, except a slight increase observed for serotype 1 after the third vaccination (22.8 to 38.1 1/dil). For the Dengue Vaccine Group, baseline GMTs were similar to those of the Control Group, but showed a considerable increase after the second and the third dengue dose (neutralizing antibodies in samples collected 28 days after the first vaccination was not titrated with PRNT): from baseline to after the second and third dengue dose respectively, from 17.4 to 125 and 179 1/dil for serotype 1; from 14.4 to 151and 178 1/dil for serotype 2; from 16.4 to 155 and 190 1/dil for serotype 3; and from 8.12 to 144 and 184 1/dil for serotype 4. A strong immune response well-balanced across the four serotypes was observed after the second vaccination and confirmed after the third vaccination. Overall, the trend was similar to the one observed with the microneutralization assay but levels of neutralizing antibodies to serotype 2 were significantly lower with this method.

Age cohort comparison: With the microneutralization assay, the GMTs for serotypes 1 and 4 were slightly higher in the younger cohort than in the older cohort. The GMTs for serotype 3 were similar in the younger and the older cohort. Differences of GMTs for serotype 2 were not assessable. With the PRNT, the GMTs for all 4 serotypes were slightly higher in the younger cohort than in the older cohort.

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