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A Health Literate Patient-focused Approach to the Redesign of the Raltegravir (ISENTRESS) Pediatric Kit and Instructions for Use

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Background: Limited data exist regarding how medications for pediatric use can be developed to minimize medication errors. The integrase inhibitor raltegravir was developed for use in neonates (≥2 kg). Anticipating that neonatal administration would be performed primarily by mothers with varying degrees of health literacy, a health literate, patient-focused, iterative process was conducted to update/redesign the raltegravir granules for oral suspension pediatric kit and instructions for use (IFU) for neonatal use to be ready for regulatory submission.

Methods: Prototypes of an updated/redesigned raltegravir IFU were systematically assessed through multi-stage, iterative testing and evaluation involving untrained lay individuals with varying levels of health literacy, healthcare professionals and health literacy experts.

Results: This iterative process resulted in numerous refinements to the IFU and kit, including wording, layout, presentation, colored syringes and additional instructional steps. The revised raltegravir pediatric kit and IFU (to include neonatal dosing) were approved by the US Food and Drug Administration in 2017 and the European Union in 2018. No reported medication errors related to IFU utilization had been reported as of March 2021, reflecting >3 years of commercial use worldwide.

Conclusions: This patient-focused process produced health literate instructions for preparing and administering an antiretroviral for neonatal use with complex dosing requirements. Testing demonstrated that lay users with a range of health literacy levels were able to accurately mix, measure and administer the product. This process demonstrates how a neonatal medication can be optimized for use through collaboration between the infectious disease expert community and a manufacturer.

Key Words: raltegravir, neonatal, pediatric, instructions for use, health literacy, patient-focused, patients, health literate, product labeling, patient labeling, medication safety, pediatric dosing, HIV

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Rapid initiation of antiretroviral (ARV) therapy is now recommended for all children diagnosed with HIV,[1] including neonates, who have unique and rapidly changing physiologic considerations that affect drug pharmacokinetics and pharmacodynamics.[2,3] This can lead to relatively complex dosing regimens, creating challenges for proper home administration of neonatal ARVs by mothers or other caregivers who may be unfamiliar with medical equipment and terminology.

Personal health literacy, "the degree to which individuals have the ability to find, understand and use information and services to inform health-related decisions and actions for themselves and others,"[4] has been increasingly recognized as an important determinant of proper medication usage.[5] Lower levels of health literacy typically correlate with poor numeracy* which is also important for accurate dosing. It has been reported that >40% of parents and caregivers administering medications to children make dosing errors, many of which are correlated with low health literacy.[5] A study assessing medication errors among neonates administered prescription oral liquid medications by a mother or grandmother found dosing errors in 54% of cases.[6]

A high prevalence of limited health literacy has been noted among individuals with HIV infection, which would include the mothers who are most likely to be giving ARV medication to neonates.[7–9] Further, many families affected by HIV have disproportionately low income with limited resources,[10] factors correlated with low health literacy.[11] One study in Mozambique found a significant correlation between poor health literacy and dosing errors when measuring liquid zidovudine.[7]

The Food and Drug Administration (FDA) receives >100,000 reports of medication errors each year, ranging from trivial to fatal.[12] In recent years methods to reduce medication errors have been a focus of researchers as well as regulators. Patient-friendly packaging, labeling and product information are core elements of the FDA recommendations to mitigate the risk of harm to patients.[13] The US Department of Health and Human Services "Healthy People 2030" initiative addresses, for the first time, "organizational health literacy," emphasizing that "producers of health information and services have a role in improving health literacy."[4]

This article describes the methods used by the manufacturer of an ARV to redesign and optimize user-friendly packaging and usage instructions using a universal health literacy precautions approach to facilitate accurate administration to neonates, recognizing its expected use by lay caregivers with varying degrees of health literacy.

GOALS AND CHALLENGES OF REDESIGNING THE RALTEGRAVIR PEDIATRIC KIT AND INSTRUCTIONS FOR USE

In 2013, the integrase strand transfer inhibitor raltegravir (ISENTRESS, Merck & Co., Inc., Kenilworth, NJ, USA) was FDA approved for infants as young as 4 weeks of age as granules for oral

*The ability to understand and work with numbers.

suspension and provided as a pediatric kit designed for weight-based dosing beginning at 20 mg twice daily. However, the old raltegravir pediatric kit was not designed for use in neonates who required doses below 20 mg and who present a very different metabolic environment. The IMPAACT P1110[14] study developed pharmacokinetic and safety data for raltegravir in neonates, and in 2017, raltegravir received FDA approval for use in full-term infants from birth to 28 days old (neonates) weighing at least 2 kg.[15] The recommended raltegravir dosing for neonates begins as low as 4 mg once daily and is modified based upon the age (by week) and body weight of the neonate (Table 1). The dosing regimen is complex and takes into account both metabolic changes and the risk of hyperbilirubinemia in the neonate.

The smaller doses that accompanied the new neonatal approval necessitated adjusting the concentration of the reconstituted oral suspension and changes in syringe quantity and sizing. The old kit included two 5-mL syringes (see Fig. 1), which adequately served the prior range of approved pediatric dosing for infants 4 weeks and older at the reconstituted suspension concentration of 20 mg/mL, with 1 mL as the lowest dose volume. Feedback from IMPAACT P1110 clinical investigators indicated that the 20 mg/mL concentration would be challenging to use given the very small doses anticipated for neonates (eg, a 4 mg dose would be 0.2 mL). Accordingly, a more dilute final concentration (10 mg/mL) was implemented to facilitate the full scope of pediatric dosing recommendations of the granules [0.4 mL (4 mg) to 10 mL (100 mg)], along with 3 different syringe sizes (1-mL, 3-mL and 10-mL).

These kit modifications were necessary but greatly increased the kit's complexity for use across multiple ages and weight bands. Given that newborns receiving raltegravir typically are sent home shortly after birth, the instructions for use (IFU) needed to be easily understood by mothers and other lay caregivers. Consequently, plans were made to purposefully redesign the pediatric kit and IFU to ensure the instructions were easily understandable and executable for all users to maximize the likelihood of proper preparation and administration and to minimize risks for harm. This required consideration of a wide range of possible health literacy proficiencies, as well as the consideration that most users would be mothers with HIV facing the added stress of caring for an HIV-exposed or infected newborn.

Between the approval of the original raltegravir pediatric granules and the expanded neonatal indication, FDA newly required human factors testing in certain situations.[16] Human factors studies (formative studies and validation studies) evaluate the ability of typical users to appropriately and safely measure and administer medication.

TABLE 1. Recommended Dose for Raltegravir Oral Suspension in Full-term Neonates [Birth to 4 weeks (28 days) of Age][a]

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week – once daily dosing*	
2 kg to <3 kg	0.4 mL (4 mg) once daily
3 kg to <4 kg	0.5 mL (5 mg) once daily
4 kg to <5 kg	0.7 mL (7 mg) once daily
1 to 4 weeks – twice daily dosing†	
2 kg to <3 kg	0.8 mL (8 mg) twice daily
3 kg to <4 kg	1.0 mL (10 mg) twice daily
4 kg to <5 kg	1.5 mL (15 mg) twice daily

*The dosing recommendations are based on approximately 1.5 mg/kg/dose.

†The dosing recommendations are based on approximately 3 mg/kg/dose.

[a]If the mother received raltegravir 2–24 hours before delivery, the neonate's first dose should be given between 24 and 48 hours after birth.

RALTEGRAVIR KIT AND IFU REDESIGN PROCESS

A comprehensive, systematic, multi-disciplinary, iterative strategy was developed to redesign and optimize the raltegravir granules for the oral suspension pediatric kit and the accompanying IFU. This process involved extensive critique, testing and input from health literacy experts, HIV-experienced healthcare providers, leaders from the raltegravir clinical trials and lay individuals with varying levels of health literacy and similar demographics to anticipated users (Fig. 2).

Determination of Likely Users

It was imperative to identify the likely users of the raltegravir kit to optimize the design. Feedback from IMPAACT P1110 study investigators and focus groups comprised of healthcare professionals (physicians, nurses and pharmacists engaged in neonatal HIV care) led to an understanding that mothers or other lay caregivers of HIV-infected newborns would be most likely responsible for reconstitution and administration.

Instructions for Use

The revised IFU content was tested in both leaflet and booklet formats, initially among lay individuals with no previous experience with raltegravir preparation. Volunteers were screened using validated health literacy assessments to ensure the inclusion of individuals with a range of health literacy levels.

Eye-tracking technology was used to measure and analyze eye movement while reading the IFU prototype. Eye-tracking data indicated difficulty following the instructional flow in text-heavy areas. The layout was adjusted in response, including text simplification and proximity to corresponding graphics. Also, text/graphics combinations that caught users' attention were noted and similar design concepts were applied in other areas of the IFU.

Feedback from IMPAACT P1110 study investigators indicated graphics used to illustrate a water source for reconstitution (a tap or faucet) may not be applicable for all locales and suggested adding a bottled water graphic. The investigators also emphasized that grandparents were likely to be among the regular caregivers and that the written materials should be designed accordingly (eg, larger text).

Given the importance of health literacy principles for ensuring broad usability, the printed IFU materials were evaluated by health literacy experts from Northwestern University (Michael Wolf, PhD, MPH; Julia Yoshino Benavente, MPH) and Emory University (Ruth Parker, MD; Kara Jacobson, MPH), who also led independent focus groups with teams from their respective organizations to identify potential challenges that untrained users might encounter. These experts then helped lead focus group-type discussions with lay individuals including people with limited health literacy to optimize the IFU language and layout. Table 2 outlines key features integrated into the final IFU based on input from health literacy experts.

Initially, collective focus group feedback (healthcare professionals and lay users) indicated a subjective preference for the leaflet format; the booklet was viewed as lengthy with too many steps. User performance with the leaflet and booklet IFU formats was compared objectively (eg, errors and close calls during use of the product) through human factors formative studies conducted with lay volunteers of varying degrees of health literacy. Counter to subjective preferences for the leaflet, findings revealed fewer errors with the booklet format which more easily constrained the user to perform tasks in the correct sequence. Given that accuracy and performance were considered the most important outcomes, the final IFU was designed as a booklet.

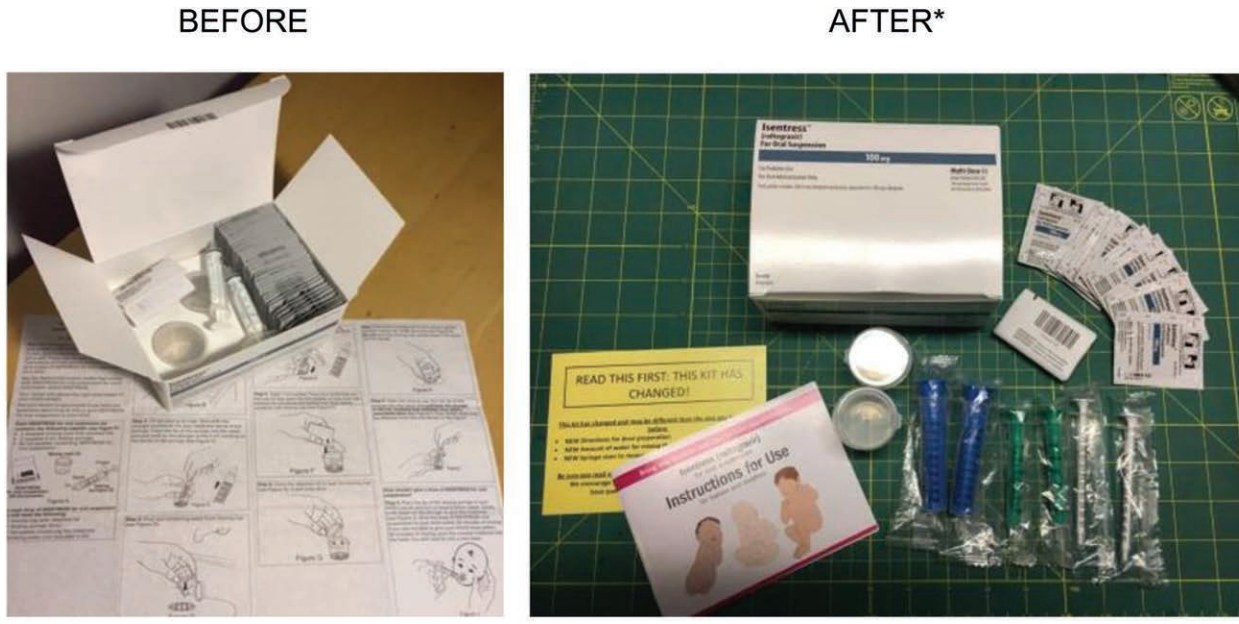

FIGURE 1. ISENTRESS Oral Suspension Kit Components before and after the redesign process (US labeling). *Actual kit contains 60 packets of ISENTRESS granules for suspension.

Healthcare providers commonly advised that caregivers benefit from multiple supporting resources, including videos that may be particularly helpful for users with low health literacy (and also as a backup if the printed materials are misplaced). A video was developed based on US labeling and accessible from the US ISENTRESS website[17] to lead users/caregivers through the instructions. In response to healthcare providers' emphasis on the importance of clinical staff training, a statement was placed prominently at the beginning of the IFU stating that users should first observe a doctor demonstrate how to prepare and administer the product.

Kit Components

Revision of the kit materials to support neonates required the replacement of 5-mL syringes supplied in the old kit with 1-mL, 3-mL and 10-mL syringes (2 of each size). The engineering team, over several iterations, redesigned the printing on the syringe to minimize medication errors and enable ease of use, guided by input from health literacy experts. Each syringe size was of a unique color and identified in the IFU by color in addition to mL capacity, facilitating numeracy. Color combinations that are commonly confounded in color blind individuals (eg, red/green and blue/yellow) were purposely avoided. All dose volumes were displayed as printed characters on the syringes to avoid the need for users to interpret unlabeled graduation lines. Also, the printed doses used leading zeros before the decimal point with no trailing zeros. Syringe measurement markings were aligned directly with the IFU and shown only as mL-based units (rather than teaspoons and mL), design aspects shown to reduce pediatric dosing errors.[18] Human factors testing confirmed that sufficient contrast existed between the mixed suspension and the syringe measurement markings to allow users to accurately draw up the volumes.

It was considered very important that users of the old pediatric kit be made aware of the different concentrations of the reconstituted raltegravir in the redesigned kit. In the US market, a bright yellow notification card summarizing the kit changes in simple language was developed. The card was placed such that users would be required to view the information before dose preparation.

Validation of the Revised Kit and IFU

Before market introduction, human factors validation studies were conducted to assess whether caregivers understood the instructions and could reliably prepare proper medication dosages. This work determined that the revised kit and IFU appeared to acceptably minimize risks of a medication dosing error, even with the added complexity resulting from the neonatal indication. The revised raltegravir pediatric kit was approved by the FDA on November 22, 2017, and subsequently by the European Commission on March 3, 2018 (note: due to differing regulations, revised kit materials in the EU are slightly different). The FDA-approved IFU content can be viewed online.[19]

The performance of the revised kit has been monitored by standard pharmacovigilance practices, which provide an ongoing assessment of adverse event reporting, including errors in dosing. As of March 2021, there had been no reports associated with the interpretation and utilization of the IFU.

DISCUSSION

Clear and health literate patient materials and drug packaging are among FDA recommendations to mitigate the risk of harm to patients.[20] Here we describe a collaborative, multidisciplinary process that addressed a critical need for user understandability and accuracy for an important medical product in an at-risk pediatric population and the iterative, health literate-focused approach that achieved that goal. The revised raltegravir for oral suspension kit has been recognized by the French journal, *Prescrire* as a recipient of its 2019 "Packaging Award."[20] The journal cited a "wealth of useful information to help prevent errors" and that the booklet "is an example of what ought to be the rule, due to the effort invested in providing unambiguous, easy-to-follow instructions." As of March 2021, no medication

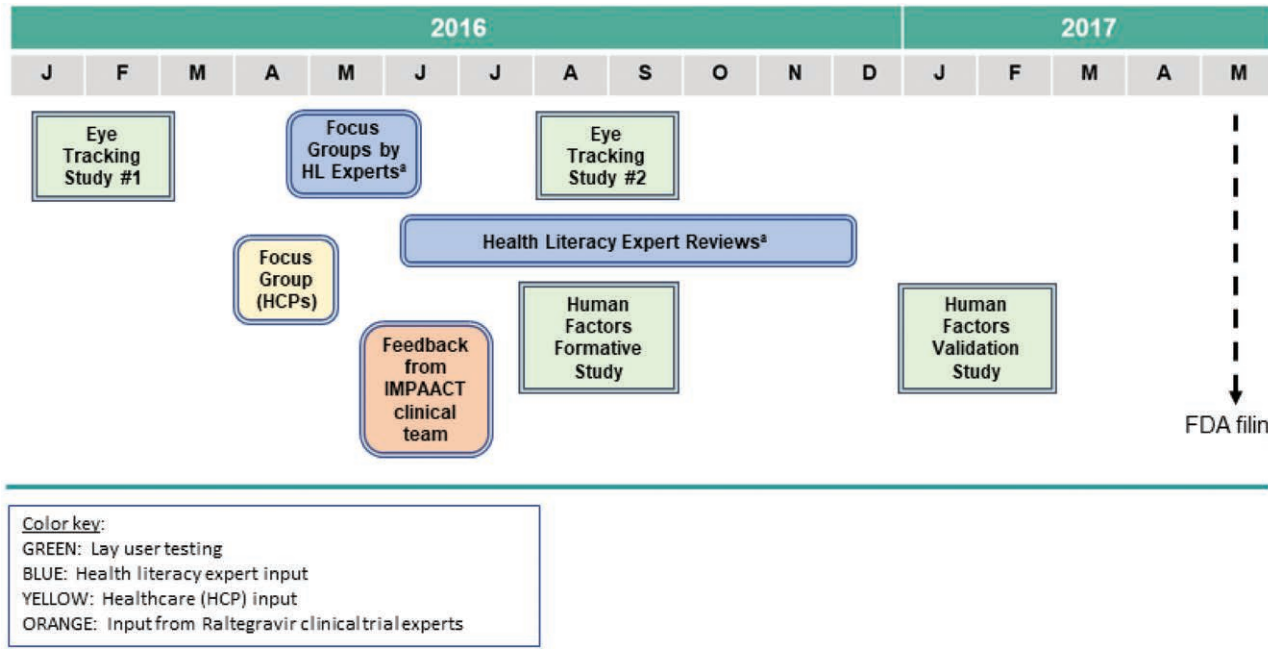

FIGURE 2. Multi-disciplinary steps involved in the redesign of the raltegravir oral suspension kit and instructions for use. [a]Health literacy experts from Northwest University and Emory University. HCPs, healthcare practitioners; HL, health literacy; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network.

errors in the use of this raltegravir formulation for neonatal patients had been reported.

The refinement and development of the kit and IFU included testing and input from a wide range of individuals and perspectives, including untrained lay individuals with varying degrees of health literacy, experienced healthcare professionals, health literacy experts and the corporate product development team. Each of these groups provided unique and valuable perspectives and the sequential learnings led to cumulative improvements. Reliance on the expertise of health literacy specialists and testing individuals with a range of health literacy levels throughout the process was inarguably critical and likely accounts for the lack of dosing errors reported. The final product featured and emphasized the use of graphics rather than just text, which is a known strategy for enhancing understanding and overcoming health literacy challenges.[21] Almost every detail of the kit, down to syringe sizes, graduation markings, colors, page breaks in the booklet, language usage and graphics coordinated with the kit materials, was evaluated and tested to improve user accuracy. The input of medical and health literacy experts was critical for initial product design; however, human factors testing with lay individuals were the ultimate test of the success and usability of the materials. The value of human factors testing was highlighted when the initial subjective preference expressed by healthcare professionals and lay users for the leaflet

TABLE 2. Key Features of the Redesigned Raltegravir Oral Suspension Kit and Instructions for Use (IFU) Driven by the Iterative Developmental Process, Including Input from Health Literacy Experts

Kit Components
1. Addition of 4 additional oral syringes (total of 6 syringes, 3 sizes with an extra of each)
2. Syringes are color-coded, avoiding most common color blindness color pairings for syringe and plunger
3. Dose volume measurements are displayed as printed characters on dosing syringe
IFU
1. Incorporation of health literacy principles
Simplified product name (eg, simply "ISENTRESS" rather than "ISENTRESS for oral solution")
Color and bolding for emphasis
Headings and adequate white space to organize the material and focus the user's attention
Simple, conversational language:
-"doctor" rather than "healthcare provider"
-"throw away" instead of "discard"
2. Color graphics and image of babies on the cover of the IFU booklet to engage the user
3. Key instructions presented close to each figure and diagrams provide the user with visual cues for each step
4. Visuals that are complementary to the text but also instructive on their own
5. Booklet format constrains the user to perform tasks in the correct sequence
6. Page spreads were planned to avoid flipping a page whilst performing fine motor tasks such as measuring
7. Additional steps to add clarity (ie, eliminating air bubbles)
8. Challenges with numbers/numeracy addressed by graphics showing which syringe for dose range
9. Syringes referred to by color rather than mL size (eg, "blue syringe" rather than "10 mL syringe")

IFU, instructions for use

IFU format was subsequently eclipsed by the results of user testing which revealed fewer errors with the booklet format.

While the process described herein was specific to the US, a heavy reliance on health literacy principles can facilitate cross-cultural modification. Beginning with a health literate version facilitates understandability when documents are later translated and culturally adapted. The booklet has already been translated into multiple languages for use in the EU market.

Following FDA and EU approval, assessments were made as to whether the kit would be suitable for use in resource-limited environments. In a World Health Organization (WHO)-sponsored study at an HIV clinic in Durban, South Africa,[22] 34 lay caregivers participated in a study to evaluate the acceptability and feasibility of preparing raltegravir granules utilizing the instructions provided with the kit after being counseled by a nurse, pharmacist or lay (nonmedical) person. Caregivers were evaluated right after the training and re-evaluated after practicing with dummy medication at home for 5–7 days. The participants liked the booklet and especially appreciated the pictures as the English instructions were not well understood by many of them. In that study, fewer errors occurred when training was provided by nurses or pharmacists rather than by laypersons, emphasizing the importance of training by healthcare providers. Further, practice and use of the illustrated IFU were identified as positive factors in improving drug preparation and administration, and it is likely that the premarket human factors testing with individuals of low health literacy were instrumental in the eventual development of a tool with broad applicability. This usability assessment in South Africa supported the inclusion of raltegravir granules for oral suspension on the current WHO list of essential medications for children.[23]

The raltegravir kit redesign project contributed generalizable knowledge applicable for the development of other medical products administered by patients and caregivers. A medication kit comprised of commonly used oral syringes should not be viewed as a simple or non-technical product development exercise. The development team should be expanded beyond the product engineers to include clinical researchers, academic partners with expertise in health literacy and healthcare professionals to gain deeper insights. It is critical to actively seek an accurate understanding of the attributes and capabilities of the user of the product and keep these top-of-mind throughout the development process. A successful strategy should commit to iterative design and the conduct of purposeful studies to investigate various attributes of the product-user interface, while taking steps to ensure representativeness of the intended users in the study panels.

In summary, this case example illustrates how thoughtful, cross-disciplinary and health literate-focused product development can contribute to quality patient care, in this case in a vulnerable pediatric population. Such efforts are intended to support healthcare providers and provide reassurance to prescribers that patients will be best prepared to administer a neonatal HIV medication, regardless of the caregiver's level of health literacy. We hope that the process and learnings described here might be useful as a case example for developing other products with potentially complex dosing or administration and for which use by lay individuals is anticipated.

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Current Abstracts

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Incidence Rates, Household Infection Risk and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York

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Differences have been observed in SARS-CoV-2 infection frequency and clinical presentation among children compared with adults since the earliest months of the COVID-19 pandemic. In early case series of SARS-CoV-2 infections, children accounted for a minority of cases, which raised questions about whether children were tested for SARS-CoV-2 less frequently than adults because of differences in clinical presentation, care seeking or access to testing; had fewer opportunities for exposure because of prevention measures; or in fact were less susceptible to infection because of differences in baseline immune status. Multiple studies have now suggested that children are more likely than adults to have asymptomatic or atypical SARS-CoV-2 infections that may not meet COVID-19 case definitions. At the same time, seroprevalence, household, outbreak and surveillance studies have now clearly established that children are susceptible to SARS-CoV-2. However, findings remain mixed with respect to the relative risk of infection among children compared with adults.

The Coronavirus Household Evaluation and Respiratory Testing (C-HEART) study follows up households with one or more children 0–17 years old in Utah and New York City, New York, with an intensive surveillance approach that includes weekly systematic molecular testing for both symptomatic and asymptomatic SARS-CoV-2 infections. Using interim data from this prospective cohort, incidences of SARS-CoV-2 infections among children and adults were estimated and compared, cumulative household infection risk was estimated and clinical features of infections by age were compared during a period of increased SARS-CoV-2 circulation.

A total of 1236 participants in 310 households participated in surveillance, including 176 participants (14%) who were 0–4 years, 313 (25%) 5–11 years, 163 (13%) 12–17 years and 584 (47%) 18 years of age or older. Overall incidence rates of SARS-CoV-2 infections were 3.8 (95% confidence interval [CI], 2.4–5.9) and 7.7 (95% CI 4.1–14.5) per 1,00 person-weeks among the Utah and New York City cohorts, respectively. Site-adjusted incidence rates per 1000 person-weeks were similar by age group: 6.3 (95% CI, 3.6–11) for children 0–4 years, 4.4 (95% CI, 2.5–7.5) for children 5–11 years, 6.0 (95% CI, 3.0–11.7) for children 12–17 years and 5.1 (95% CI, 3.3–7.8) for adults 18 years of age and older.

The asymptomatic fractions of infection by age group were 52%, 50%, 45% and 12% among individuals 0–4, 5–11, 12–17 and 18 years of age or older, respectively. Among 40 households with one or more SARS-CoV-2 infections, the mean risk of SARS-CoV-2 among all enrolled household members was 52% (range, 11%–100%), with higher risks in New York City compared with Utah (80% [95% CI, 64%–91%] vs. 44% [95% CI, 36%–53%], *P* less than 0.001).

Comment: In this study, children had similar incidence rates of SARS-CoV-2 infection compared with adults, but a larger proportion of infections among children were asymptomatic. It remains unclear how risk of SARS-CoV-2 infection among adults and children will evolve with increasing COVID-19 vaccine uptake among adults, COVID-19 vaccination policies for children, and increasing circulation of SARS-CoV-2 variants of concern. The findings in this report suggest that SARS-CoV-2 infection prevention strategies, such as hand hygiene, masking, social distancing and COVID-19 vaccination should target children in addition to adults to both mitigate individual health outcomes for children and reduce the overall burden of SARS-CoV-2 infection in the community.