A Health Literate Patient-focused Approach to the Redesign of the Raltegravir (ISENTERRESS) 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 literacy, product labeling, patient labeling, medication safety, pediatric dosing, HIV

Rapid initiation of antiretroviral (ARV) therapy is now recommended for all children diagnosed with HIV, including neonates, who have unique and rapidly changing physiologic considerations that affect drug pharmacokinetics and pharmacodynamics. 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,” has been increasingly recognized as an important determinant of proper medication usage. 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. A study assessing medication errors among neonates administered oral liquid medications by a mother or grandmother found dosing errors in 54% of cases.

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. Further, many families affected by HIV have disproportionately low income with limited resources, factors correlated with low health literacy. One study in Mozambique found a significant correlation between poor health literacy and dosing errors when measuring liquid zidovudine.

The Food and Drug Administration (FDA) receives >100,000 reports of medication errors each year, ranging from trivial to fatal. 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. 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.”

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 (ISENTERRESS, 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 20mg twice daily. However, the old raltegravir
pediatric kit was not designed for use in neonates who required doses
below 20mg and who present a very different metabolic environment.
The IMPAACT P1110 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 (neo-
ates) weighing at least 2kg. The recommended raltegravir dosing
for neonates begins as low as 4mg 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 re-
constituted oral suspension and changes in syringe quantity and siz-
ing. The old kit included two 5mL syringes (see Fig. 1), which
adequately served the prior range of approved pediatric dosing for
infants 4 weeks and older at the reconstituted suspension concen-
tration. 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 concen-
tration of 20mg/mL, with 1mL as the lowest dose volume. Feed-
back from IMPAACT P1110 clinical investigators indicated that
the 20mg/mL concentration would be challenging to use given the
very small doses anticipated for neonates (eg, a 4mg dose would be
0.2mL). Accordingly, a more dilute final concentration (10mg/mL)
was implemented to facilitate the full scope of pediatric dosing rec-
ommendations of the granules [0.4mL (4mg) to 10mL (100mg)],
along with 3 different syringe sizes (1mL, 3mL and 10mL).

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 eas-
ily 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 execut-
able 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 proficien-
cies, 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 pediat-
ric granules and the expanded neonatal indication, FDA newly
required human factors testing in certain situations. Human fac-
tors 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]*

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

*The dosing recommendations are based on approximately 1.5mg/kg/dose.
†The dosing recommendations are based on approximately 3mg/kg/dose.
‡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 accompa-
nying IFU. This process involved extensive critique, testing and input
from health literacy experts, HIV-experienced healthcare provid-
ers, 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 raltegra-
vin kit to optimize the design. Feedback from IMPAACT P1110
study investigators and focus groups comprised of healthcare pro-
fessionals (physicians, nurses and pharmacists engaged in neonatal
HIV care) led to an understanding that mothers or other lay caregiv-
ers 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 book-
let formats, initially among lay individuals with no previous experi-
ence 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 indi-
cated 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 ensur-
ing 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 organi-
sations to identify potential challenges that untrained users might
encounter. These experts then helped lead focus group-type discus-
sions with lay individuals including people with limited health lit-
eracy 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 pro-
fessionals 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 per-
formance were considered the most important outcomes, the final
IFU was designed as a booklet.
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 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. 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.

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. 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.” 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

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**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.
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

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**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 | IFU |
|----------------|-----|
| 1. Addition of 4 additional oral syringes (total of 6 syringes, 3 sizes with an extra of each) | 1. Incorporation of health literacy principles |
| 2. Syringes are color-coded, avoiding most common color blindness color pairings for syringe and plunger | Simplified product name (eg, simply “ISENTRESS” rather than “ISENTRESS for oral solution”) |
| 3. Dose volume measurements are displayed as printed characters on dosing syringe | 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 “10mL syringe”) |

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*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, 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. 21 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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REFERENCES

1. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed May 19, 2021.
2. O’Brien F, Clapham D, Krysiak K, et al. Making medicines baby size: the challenges in bridging the formulation gap in neonatal medicine. Int J Mol Sci. 2019;20:2688.
3. Clarke DF, Pennazato M, Capparelli E, et al; WHO Paediatric Antiretroviral Working Group. Prevention and treatment of HIV infection in neonates; evidence base for existing WHO dosing recommendations and implementation considerations. Expert Rev Clin Pharmacol. 2018;11:83–93.
4. US Department of Health and Human Services: Office of Disease Prevention and Health Promotion. Healthy people 2030. Health literacy in healthy people. Available at: https://health.gov/our-work/healthy-people-2030/about-healthy-people-2030-health-literacy-healthy-people. Accessed September 1, 2020.
5. Williams TA, Wolf MS, Parker RM, et al. Parent dosing tool use, beliefs, and access: a health literacy perspective. J Pediatr. 2019;215:244–251.e1.
6. Solanki R, Mondal N, Mahalakshmy T, et al. Medication errors by caregivers at home in neonates discharged from the neonatal intensive care unit. Arch Dis Child. 2017;102:651–654.
7. Howard LM, Tique JA, Garside S, et al. Health literacy predicts pediatric dosing accuracy for liquid zidovudine. AIDS. 2014;28:1041–1048.
8. Waldrop-Valverde D, Murden RJ, Guo Y, et al. Racial disparities in HIV antiretroviral medication management are mediated by health literacy. Health Lit Res Pract. 2018;2:e205–e213.
9. Walker RL, Hong JH, Talavera DC, et al. Health literacy and current CD4 cell count in a multiethnic U.S. sample of adults living with HIV infection. J Int Stud AIDS. 2018;29:498–504.
10. Pellow JS, Kalichman SC, Matthews KA, et al. A pandemic of the poor: social disadvantage and the U.S. HIV epidemic. Am Psychol. 2013;68:197–209.
11. Kutner M, Greenberg E, Jin Y, et al. The Health Literacy of America’s Adults: Results from the 2003 National Assessment of Adult Literacy (NCES 2006–485). U.S. Department of Education. Washington, DC: National Center for Education Statistics; 2006.
12. U.S. Food and Drug Administration. Working to reduce medication errors. Available at: https://www.fda.gov/drugs/drug-information-consumers/working-reduce-medication-errors. Accessed September 24, 2020.
13. U.S. Department of Health and Human Services. Safety considerations for product design to minimize medication errors: guidance for industry. Available at: https://www.fda.gov/media/84903/download. Accessed September 24, 2020.
14. Clarke DF, Acosta EP, Cababassy M, et al; IMPAECT P1110 Protocol Team. Raltegravir (RAL) in neonates: dosing, pharmacokinetics (PK), and safety in HIV-1-exposed neonates at risk of infection (IMPAECT P1110). J Acquir Immune Defic Syndr. 2020;84:70–77.
15. Merck & Co., Inc. Press Release: Merck receives FDA approval for ISENTRESS® (raltegravir), in combination with other antiretroviral agents, for the treatment of HIV-1 infection in newborns weighing at least 2 kg. Merck & Co., Inc., Kenilworth, NJ USA. Available at: https://www.merck.com/news/merck-receives-fda-approval-for-istemress-raltegravir-in-combination-with-other-antiretroviral-agents-for-the-treatment-of-hiv-1-infection-in-newborns-weighing-at-least-2-kg/. Accessed September 24, 2020.
16. US Department of Health and Human Services: Food and Drug Administration. Human factors studies and related clinical study considertions in combination with product design and development: Draft guidance for industry and FDA staff. 2016. Available at: https://www.fda.gov/media/96018/download. Accessed August 1, 2019.
infections among children and adults were estimated and compared, interim data from this prospective cohort, incidences of SARS-CoV-2 for both symptomatic and asymptomatic SARS-CoV-2 infections. Using surveillance approach that includes weekly systematic molecular testing 0–17 years old in Utah and New York City, New York, with an intensive (C-HEART) study follows up households with one or more children among children compared with adults.

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 presentations 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 presentations.

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 < 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.

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 1,000 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.

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