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DIABETIC Medicine

LETTER

Evaluation of protocol amendments to the Environmental Determinants of Islet Autoimmunity (ENDIA) study during the COVID-19 pandemic

The Environmental Determinants of Islet Autoimmunity (ENDIA) Study is an Australia-wide observational pregnancy-birth cohort of children at genetic risk on account of a first-degree relative with type 1 diabetes.[1] A total of 1511 participants were recruited from all Australian States and Territories from 2013 to 2019 with 1473 live-born infants in follow-up. The standard protocol involves 3-monthly face-to-face visits from pregnancy until the child is 2 years of age, then 6-monthly visits. Study staff across nine centres in five States collect biospecimens (blood, urine, stool, swabs) and administer lifestyle and dietary questionnaires. Approximately 10% of the cohort are engaged in a Regional Participant Program[2] that requires self-collection of sample types except for venepuncture performed at local pathology services.

As COVID-19 case numbers increased across Australia from March 2020,[3] hospitals and institutions placed varying degrees of restriction on interactions with research participants. Concurrently, the introduction of early and high-level social distancing measures correlated with a markedly lower frequency of respiratory infections in Australian children.[4] This abrupt change is relevant to ENDIA as respiratory and other viral infections have been implicated in type 1 diabetes development.[5]

We rapidly used a COVID-19 framework for the conduct of study visits commencing 23 March 2020 when the median age of the cohort was 2.5 (IQR 1.3,3.8) years. Here, we outline these protocol amendments and evaluate their efficacy in the 9 months before and after implementation. The amendments were approved by the lead HREC (project HREC/16/WCHN/66).

The COVID-19 framework provided seven increasing risk-based levels of operation ranging from standard pre-COVID practices (Levels 1 and 2 for clinic and home visits) to a complete shutdown (Level 7). A copy of the framework can be located: https://doi.org/10.25909/14544636. Sites were able to independently escalate or de-escalate operations according to local epidemiological risk as assessed by the Principal Investigator and/or institutional directives.

We evaluated the impact of these protocol changes on the numbers of conducted study visits with biospecimen collection over an 18-month period. Time spans were defined as 'pre-COVID': 24 June 2019 to 22 March 2020 (39 weeks), and 'COVID': 23 March to 20 December 2020 (39 weeks). The numbers of theoretical visits were determined according to age and included projected pregnancy, birth and child visits. A Poisson regression allowing attendance rate to be modelled was fitted using R (V3.6.3). The response was the actual number of visits with a log offset of the theoretical number of visits. For stool, blood and swab collection rates, the response was the actual number of specimens collected with a log offset of the actual number of visits. Differences between pre-COVID and COVID were determined by including a categorical variable in the model. From March to May 2020, all study sites across Australia were operating between Levels 5 and 7 of the COVID-19 framework. At Level 5, venepuncture was limited to children known to have islet or coeliac autoimmunity and performed using full personal protective equipment. The majority of visits were at Level 6 with self-collected stool and skin, nasal and oral swabs and no blood samples. When restrictions reduced, visits were opened to Level 1–2 (no restrictions at home or clinic) at sites with no community transmission and to Levels 3–4 (blood sample taken) at sites where transmission was low. The level rose again in Victoria during the second wave of COVID-19 from June to November 2020.[6]

Actual visit attendance across the pre-COVID period was 82% of theoretical (2598/3166 overall visits) versus 78% during COVID (2015/2589 overall visits). An early drop in visit attendance recovered and was maintained during the second wave of COVID-19 cases that peaked in Victoria in late July (Figure 1a). Weekly visit attendance rates did not differ significantly pre-COVID versus during COVID ($p = 0.07$). With respect to biospecimen

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All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published. MP, HO and JJC agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

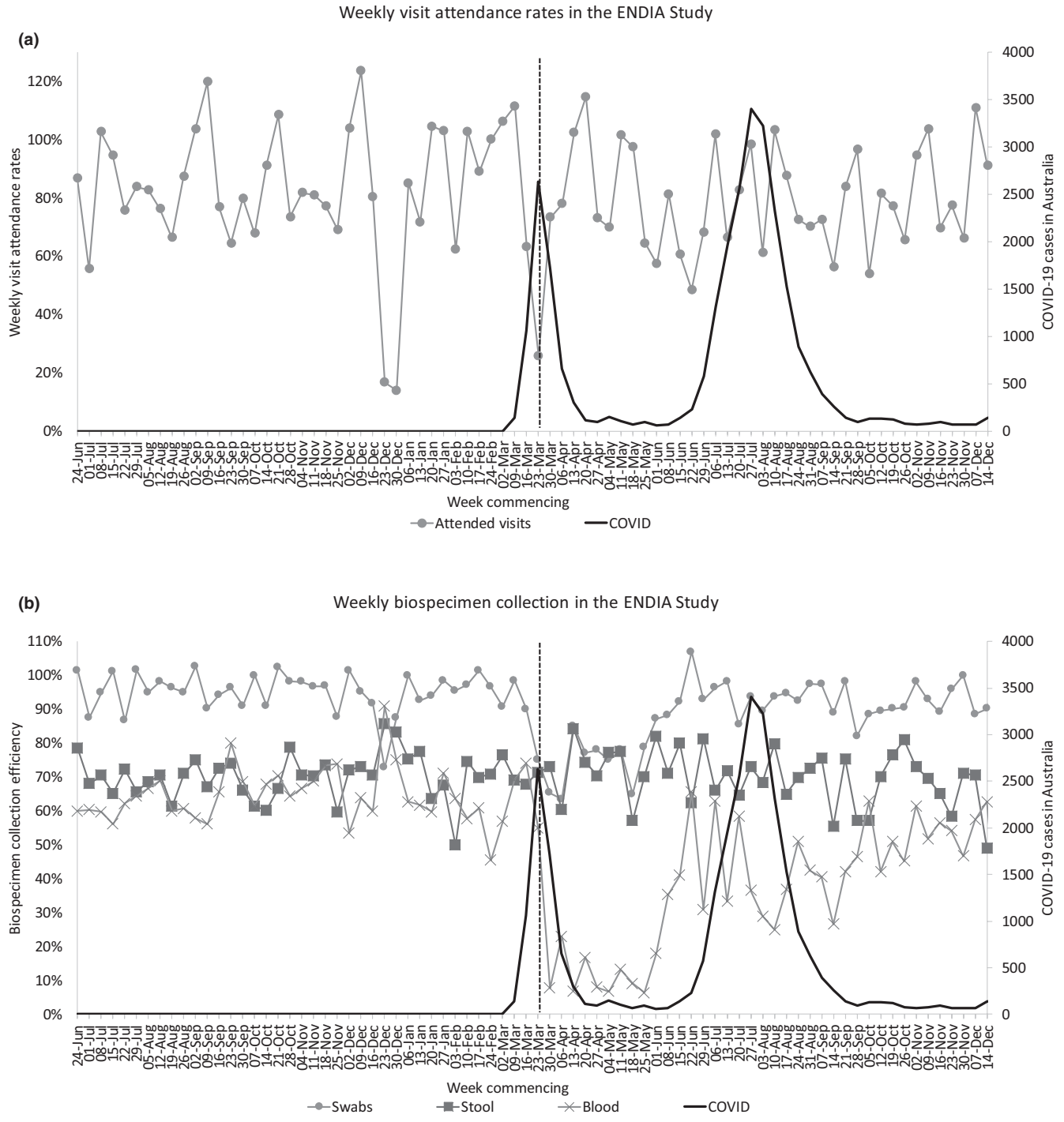

FIGURE 1 (a) Environmental Determinants of Islet Autoimmunity (ENDIA) study visit attendance rate each week between 24 June 2019 and 20 December 2020 is shown with overlaying of the number of COVID-19 cases reported in Australia.[7] (b) The proportion of study visits at which collection of blood, stool and nasal swabs occurred are shown over the same time period. Values may exceed 100% where sample collection was incongruent with the reported visit date such as for swabs that were collected the week before or after the visit to the clinic. The dashed vertical line indicates when the modified protocol was implemented defining the 'pre-COVID' and 'COVID' periods

collection (Figure 1b), compliance with stool collection was unaffected and averaged 70% across the pre-COVID and COVID time spans ($p = 0.83$). Blood collection rate pre-COVID versus COVID reduced by 44% [incidence rate ratio = 0.56 (95% CI 0.51–0.61), $p < 0.001$]. Compliance with nasal swabs reduced with self-collection and improved with increasing coordinator contact. Between pre-COVID and COVID, there was a 9% reduction in the overall swab collection rate [incidence rate ratio = 0.91 (95%CI 0.86–0.97), $p = 0.003$].

In conclusion, changes to the ENDIA protocol in response to the COVID-19 pandemic were rapidly and successfully rolled out across the network. As different Australian States and Territories had different restrictions at any given time, this flexibility was essential. Our evaluation showed that visit numbers did not significantly differ in the 9 months before versus after implementation. Overall, the capacity to modify practice with evolving epidemiological risk enabled staff to maintain data collection and a majority of biospecimen collections. Moreover, we kept families engaged when the risk of loss-to-follow-up was high. Our framework may be helpful for other observational cohort studies that have been impacted by COVID-19 restrictions.

ETHICS APPROVAL STATEMENT

The ENDIA study has been approved by the Women's and Children's Hospital Network Human Research Ethics Committee (HREC) as the lead HREC in South Australia, Queensland, New South Wales, Victoria and regional Australia under the Australian National Mutual Acceptance Scheme (reference number HREC/16/WCHN/066). Conduct in Western Australia has been approved by the Women and Newborn Health Service Ethics Committee (reference number RGS0000002639). The ENDIA study is registered on the Australia New Zealand Clinical Trials Registry (ACTRN1261300794707).

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

JJC and LCH conceived the study. MASP, AJA, RLT, KM, SCB, PGC, MEC, EAD, MH, AH, GM, WDR, ROS, GS, PJV, JMW, LCH and JJC designed the protocol amendments. MASP, AA, RT and KM disseminated and evaluated the amendments. PGC, MEC, EAD, MH, AH, GS, PJV, JMW, LCH and JJC oversaw implementation of the protocol at clinical sites. MASP compiled and interpreted the data. HO performed the statistical analysis. MASP and JJC wrote the manuscript. All authors provided critical revision of the manuscript and approved the final version. JJC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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