Rapid Review Protocol:

The association between Covid-19 and new onset of Type 1 diabetes: a rapid review

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Background and rationale

This protocol describes a review that is being undertaken to respond to a growing number of reports that there may be a relationship between infection with Covid-19 and a new diagnosis of Type 1 diabetes. We intend to synthesise the literature in order to identify what is currently known and to inform how best research using electronic health records can further explore this relationship to understand the risks and provide appropriate public health guidance.

Type 1 diabetes is a chronic condition in which the pancreas produces little or no insulin, usually due to an auto-immune response which destroys the islets of Langerhans cells in the pancreas (https://www.diabetes.org.uk/). The majority of Type 1 cases occur in childhood or adolescence. There is no cure, and treatment is reliant on replacing insulin using injections or pumps to be able to allow sugar in the bloodstream to enter the cells and control the blood glucose levels. The exact triggers for the development of Type 1 diabetes are unknown, but exposure to viruses and other environmental factors are thought to be important (Filippi and von Herrath, 2008). Seasonal variation in the incidence of new cases has often been attributed to increased viral circulation, for example associated with the return of children to schools (Turtinen et al., 2022, Nishioka et al., 2020). It is unclear whether the SARS-Coronavirus-2 virus (SARS-Cov-2), which is responsible for the Covid-19 pandemic, may influence the development of Type 1 diabetes, although evidence is emerging that there may be an association (Barrett et al., 2022).

The public health approach to controlling SARS-Cov-2/Covid-19 in the UK has varied between regions and also between children and adults. Whereas the focus of the vaccination program has been on reducing hospital admission and death, particularly in older adults and people with clinical vulnerabilities, vaccination for adolescents aged 12-17 were introduced in August/September 2021,

and a 2 dose course for children aged 5-11 in 2022. Given the high rates of Covid-19 positivity in educational establishments and the lack of other precautionary measures, such as mandatory use of face coverings, adequate ventilation and air filtration, the scope for transmission to children and subsequent sequelae, such as Long Covid, remains significant (Zimmermann et al., 2022). Additionally, the increased difficulty in accessing both primary and secondary care health services during periods of lockdown and in the post-lockdown era may have contributed to delays in diagnosis and increased severity of presentation, and this may also be reflected in the global literature.

As the pandemic continues with successive waves of new variants of the virus, with as-yet unknown effects on the immune system and long-term health, we would like to focus on the potential role of Covid-19 in the development of new-onset Type 1 diabetes as a matter of urgency, to be able to inform public health and parental decisions about vaccination and safety measures in schools, and also to inform subsequent research using large routinely collected data sources, such as the SAIL databank and the Brecon paediatric diabetes cohort. For this purpose, a rapid review is the most suitable methodology due to its resource-efficient methods of producing a quality knowledge synthesis that can guide stakeholders to future public health and/or research funding decisions.

Review question

What is known about the relationship between Covid-19 infection and new onset of Type 1 diabetes?

Review design

The rapid review will be conducted in accordance with the recent Cochrane guidance (Garritty et al., 2021).

Eligibility criteria

The review will focus on epidemiological studies using quantitative data which describe or compare patterns of new onset of Type 1 diabetes during the pandemic and/or with other periods in time at a population level, or explore associations between exposure to Covid-19 and new onset of Type 1 diabetes on an individual level. The severity of illness at the time of presentation with Type 1 diabetes for example occurrence of diabetic ketoacidosis (DKA), requirement for stepped-up or intensive care and glycosylated haemoglobin (Hba1c) levels, during the pandemic either within case series or as compared to other time periods are also of interest.

Inclusion criteria:

- Research which is focussed on the epidemiology of Type 1 diabetes during the Covid-19 pandemic, for example incidence, prevalence, severity of presentation, estimates of association and risk.
- All quantitative study designs.
- Systematic reviews of relevant studies.

- English language articles.

Exclusion criteria:

- Publication prior to January 2020.
- Studies which only include outcomes of people with Type 1 diabetes subsequently infected with Covid-19.
- Individual case reports.
- Qualitative research.

Information Sources and Search Strategy

Four bibliographic databases were searched: Medline (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials and WHO Global database of literature on coronavirus disease. Duplicate papers will be identified and removed in Endnote 20 before being uploaded to the Covidence software (https://www.covidence.org/) for screening.

In order to maximise retrieval of evidence, the concepts used were limited. An information specialist (RW) created concept tables on the three themes of (i) Covid-19, (ii) Type 1 diabetes and (iii) new diagnosis/onset. The tables were reviewed by all co-authors, which include experts in diabetes care and research, and search terms were finalised.

Comprehensive electronic search strategies were then developed for each database using a combination of relevant keywords and index headings. The search strategy was modified so that index headings relevant to each specific database were selected. A Covid-19 search filter was used for Embase and Medline (Levay and Finnegan, 2021). The final search strategy was peer-reviewed by a second information specialist using the PRESS Checklist (McGowan et al., 2016).

The full search strategies are available at https://osf.io/63yxz/

Study selection

The eligibility criteria for title/abstract screening (as described above) will be tested by the screening team by reviewing 100 abstracts and modifications made if required. Two reviewers will screen 20% of the remaining abstracts, resolve any conflicts and make any further changes to eligibility criteria. The remaining titles and abstracts will be screened by one reviewer and a second reviewer will screen all excluded abstracts, with conflicts resolved as necessary. A full-text screening form based on the eligibility criteria will be developed and tested by both reviewers for 5 articles, and then one reviewer will screen the remaining full-text articles, with the second reviewer screening all the excluded full-text articles.

Data extraction

A data extraction form will be developed which will include: lead author, year of publication, title, journal, research question/objectives (or aim of article), study design, population, data source, outcomes considered, sample size, main findings with quantitative estimates where applicable.

Data extraction will be performed by a single reviewer. Due to the potential variety of study types, the first five extractions will be reviewed by a second reviewer to check for significant omissions and adaptations to the data extraction form made where necessary.

Quality assessment

An appropriate quality assessment tool for each study design will be used to assess for risk of bias, such as the checklists developed by the Critical Skills Appraisal Programme (CASP) (https://casp-uk.net/casp-tools-checklists/). A single reviewer will rate the risk of bias focussing on the key outcomes and a second reviewer will verify judgements.

Synthesis of evidence

This review will be conducted in accordance with the Cochrane Rapid Reviews Methods Group Guidelines (Garritty et al., 2021) and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (https://prisma-statement.org/).

The results will be synthesised narratively according to the main types of research studies found and the intent of the study. For example, studies comparing incidence of Type 1 diabetes pre- and during the pandemic will be grouped, and studies examining associations between Covid-19 infection and new onset of Type 1 diabetes will be grouped. Tables summarising the data from the extraction forms will be inserted where appropriate and grouped by study type, for example incidence, severity, estimates of risk.

Acknowledgements

The search strategy was peer reviewed by Pauline Goodlad, Librarian, John Spalding Library, Wrexham Maelor Hospital, Betsi Cadwaladr University Health Board.

References

BARRETT, C. E., KOYAMA, A. K., ALVAREZ, P., CHOW, W., LUNDEEN, E. A., PERRINE, C. G., PAVKOV, M. E., ROLKA, D. B., WILTZ, J. L., BULL-OTTERSON, L., GRAY, S., BOEHMER, T. K., GUNDLAPALLI, A. V., SIEGEL, D. A., KOMPANIYETS, L., GOODMAN, A. B., MAHON, B. E., TAUXE, R. V., REMLEY, K. & SAYDAH, S. 2022. Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years - United States, March 1, 2020-June 28, 2021. *MMWR Morb Mortal Wkly Rep,* 71**,** 59-65.

FILIPPI, C. M. & VON HERRATH, M. G. 2008. Viral trigger for type 1 diabetes: pros and cons. *Diabetes,* 57**,** 2863-71.

GARRITTY, C., GARTLEHNER, G., NUSSBAUMER-STREIT, B., KING, V. J., HAMEL, C., KAMEL, C., AFFENGRUBER, L. & STEVENS, A. 2021. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. *J Clin Epidemiol,* 130**,** 13-22.

LEVAY, P. & FINNEGAN, A. 2021. The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. *medRxiv***,** 2021.06.11.21258749.

MCGOWAN, J., SAMPSON, M., SALZWEDEL, D. M., COGO, E., FOERSTER, V. & LEFEBVRE, C. 2016. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol,* 75**,** 40-6.

NISHIOKA, Y., NODA, T., OKADA, S., MYOJIN, T., KUBO, S., HIGASHINO, T., ISHII, H. & IMAMURA, T. 2020. Incidence and seasonality of type 1 diabetes: a population-based 3-year cohort study using the National Database in Japan. *BMJ Open Diabetes Res Care,* 8.

TURTINEN, M., HÄRKÖNEN, T., ILONEN, J., PARKKOLA, A. & KNIP, M. 2022. Seasonality in the manifestation of type 1 diabetes varies according to age at diagnosis in Finnish children. *Acta Paediatr,* 111**,** 1061-1069.

ZIMMERMANN, P., PITTET, L. F. & CURTIS, N. 2022. Long covid in children and adolescents. *Bmj,* 376**,** o143.