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Trends in the mortality, incidence and disability-adjusted life-years of appendicitis in EU15+ countries: an observational study of the Global Burden of Disease Database, 1990–2019

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Background: Appendicitis places a substantial burden on healthcare systems, with acute appendicitis alone being the most common abdominal surgical emergency worldwide. Further characterisation of the disease burden in EU15+ countries may help optimise the distribution of healthcare resources. The aim of this observational study was to assess the trends in mortality, incidence and disability-adjusted life-years (DALYs) of appendicitis across European Union (EU) 15+ countries between the years 1990 and 2019, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Materials and methods: Age-standardised mortality rates (ASMRs), age-standardised incidence rates (ASIRs) and DALYs data for appendicitis in males and females were extracted from the 2019 Global Burden of Disease (GBD) study. Temporal trends within the study period were analysed using Joinpoint regression analysis.

Results: The median ASMRs across EU15+ countries in 2019 were 0.08/100 000 and 0.13/100 000 for females and males, respectively. Between 1990 and 2019 the median percentage change in ASMR was −52.12% for females and −53.18% in males. The median ASIRs in 2019 for females and males were 251/100 000 and 278/100 000, respectively, with a median percentage change of +7.22% for females and +3.78% for males during the observation period. Decreasing trends in DALYs were observed over the 30-year study period, with median percentage changes of −23.57% and −33.81% for females and males, respectively, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Conclusion: Overall, a general trend of decreasing appendicitis ASMRs and DALYs was observed across EU15+ countries, despite small overall increases in appendicitis ASIRs, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. Variations in both diagnostic and management strategies over the study period are likely contributory to the changing trends.

Keywords: Appendicitis, epidemiology, incidence, mortality, trends

Introduction

Appendicitis places a substantial burden on healthcare systems globally, with acute appendicitis alone being the most common abdominal surgical emergency in the world[1]. Previous estimates report the annual incidence of appendicitis in developed countries to be between 5.7 and 50 patients per 100 000 inhabitants[2], thereby representing one of the most common causes of acute abdominal pain in children and adults. Risk factors associated with the development of appendicitis include age (most common in adolescence), obesity and male sex with a reported lifetime risk of 8.6% in males compared with 6.7% in females[3–5].

While recent epidemiological data reflect a period of stabilisation, the incidence of appendicitis has seen an overall increase since the 1990s particularly in newly industrialised nations[6], which poses a significant challenge for healthcare policymakers.

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Primarily, these challenges relate to the sizeable financial investment required to manage the condition with hospitalisation costs exceeding $3 billion in a single year in the USA alone[7].

Despite its relatively common presentation, the treatment of appendicitis remains under active debate and the discourse surrounding operative versus non-operative management remains a point of contention. Traditionally appendicectomy has been the standard and definitive treatment for acute appendicitis[8], but this approach is not without risk of surgical complications[9,10] and a growing number of studies have suggested that the majority of patients with uncomplicated acute appendicitis may be managed non-operatively using antibiotics with relatively low rates of short-term recurrence[11–14].

In recent years, several studies have investigated epidemiological trends in appendicitis[15–17] but have mostly done so with a focus on individual countries. Two recent global updates have also been published[6,18], but there have been no reports with a focus on countries with higher levels of health expenditure, nor have mortality and incidence data from the Global Burden of Disease (GBD) study been used in combination to characterise temporal trends outside of individual nations and evaluation of disability-adjusted life-years (DALYs) data is also under-investigated in the literature. As a result, it is likely that our current understanding of the evolving global picture of appendicitis is suboptimal and further characterisation of the disease burden will be necessary to improve the deployment of healthcare resources.

Therefore, the primary objective of this study was to identify and describe the trends in incidence, mortality and DALYs of appendicitis across European Union (EU) 15+ nations (Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, UK and USA) in the period from 1990 to 2019, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

HIGHLIGHTS

- This study aims to characterise the nature of epidemiological trends in the mortality, incidence and disability-adjusted life-years of appendicitis across European Union 15+ (EU15+) countries.
- Overall, a general trend of decreasing appendicitis age-standardised mortality rates and disability-adjusted life-years was observed, despite small overall increases in appendicitis age-standardised incidence rates.
- The findings suggest recent advances in both diagnostic and management strategies for appendicitis may contribute to the reduction in disease burden seen across EU15+ countries. The data provide an evidence base to support population level decision-making by key stakeholders.

Material and methods

Data source

Data extracted from the 2019 GBD study (1990–2019) were used for this retrospective analysis. In summary, the GBD is a substantial, publicly accessible source of mortality and disability data (deaths, death rates, years of life lost due to premature mortality, incidence, prevalence) for 369 diseases/injuries compiled from 204 contributing nations[19]. As part of a WHO commissioned venture, the study pools data from multiple sources including inpatient and outpatient hospital encounter data, systematic reviews, disease registries and claims data pertaining to various diseases, risk factors and procedures. The 10th iteration of the International Classification of Disease (ICD-10) coding system is used for pathological categorisation, with codes K35-K37.9 and K38.3-K38.9 relating to appendicitis. Bayesian statistical methods are employed to generate population estimates and confidence intervals for disease death rates, incidences and DALYs, which are then made available online via the GBD Results Tool - http://ghdx.healthdata.org/gbd-results-tool[20]. The full GBD methodology has been published within depth descriptions of data sources and statistical methodology[21].

Mortality data estimates for appendicitis were derived from the cause of death database and computed using the GBD Cause of Death Ensemble model (CODEm). Vital registration and verbal autopsy data were modelled alongside location-level covariates (sociodemographic index, education years per capita, health access and quality index, exposure variable for low fruit-/vegetable consumption, log lag distributed income) to produce mortality estimates. Separate modelling was conducted for male and female patients and outlying data points were excluded if violation of well-established time or age trends occurred.

Incidence estimates were generated from hospital discharge and claims data using the DisMod-MR 2.1 model which were then corrected against cause-specific mortality rate data from the CODEm analyses. Incident cases were extracted from claims data on the basis of an individual having one or more inpatient encounters with an appropriate ICD code, with any re-admission within 28 days assumed to be part of the same episode of illness. Discharge data with an appropriate primary diagnostic code were adjusted using correction factors derived from inpatient claims data to produce an estimate for the number of individuals represented by each encounter. A fibre-consumption covariate was applied as a predictive covariate to give the final estimates.

DALYs for appendicitis are calculated as the sum of years of life lost and years lived with disability. Years of life lost are calculated by multiplying the standard life expectancy at the age of death by the estimated number of deaths from appendicitis. Years lived with disability were calculated by multiplying the prevalence of appendicitis (derived from the DisMod-MR 2.1 model) by the disability-weighting for appendicitis (derived from the GBD 2013 European disability weights measurement study[19]) before correcting for co-morbidities via a microsimulation process. There were no missing data or need for imputation.

The GBD study authors assess data reliability through a 5-star scale, related to the availability and completeness of mortality data[22]. The top tier of the scale denotes greater than 85% data completeness and was awarded to ten nations included in the present study (Australia, Austria, Canada, Finland, Ireland, Italy, Norway, Sweden, UK, USA). The remaining nine nations received a 4-star grade demonstrating greater than 65% data completeness (Belgium, Denmark, France, Germany, Greece, Luxembourg, Netherlands, Portugal, Spain).

Data handling

Nation-specific age-standardised mortality rates (ASMRs), age-standardised incidence rates (ASIRs) and DALYs per 100 000

population for appendicitis were extracted by sex for each of the years 1990–2019 inclusive. Data were extracted for each of the EU15+ countries, a set of 19 nations grouped on account of comparable levels of high healthcare expenditure, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. Age-standardisation of GBD data is achieved by computing a standard population based on a non-weighted average of a percentage of the population of all countries in each 5-year age bracket in the years 2010–2035 from the United Nations Population Division's World Population Prospects (2012 revision)[23].

Absolute and relatives changes in ASMRs, ASIRs and DALYs over the observation period were calculated based on the difference between the start (1990) and end (2019) rates for males and females in each country. Annual mortality-to-incidence index (MII) was also calculated per sex in each country by dividing the ASMR by the ASIR and multiplying by 1000. The MII provides an additional estimate of case fatality rates for appendicitis and is therefore useful for comparing disease burdens across countries. The work has been reported in line with the STROCSS criteria[24], Supplemental Digital Content 1, http://links.lww.com/JS9/A582.

Statistical analysis

Temporal trends in the disease burden of appendicitis were assessed using Joinpoint regression analysis, whereby the simplest statistical model is fitted to a dataset by connecting different line segments on a logarithmic scale. These line segments are known as Joinpoints, with the simplest model (i.e. 0 Joinpoints) being an uninterrupted line. The analysis tests whether additional Joinpoints are statistically significant using a Monte Carlo permutation method and adds them to the model accordingly. For each line segment, the software also calculates the estimated annual percentage changes for each Joinpoint, with 95% CIs, to establish if there is a difference from the null hypothesis that no annual change occurs between estimates. The final model consists of a number of Joinpoints, each representing a statistically significant change in increasing or decreasing trends (p value <0.05). The estimated annual percentage changes generated allows assessment of the changes in temporal trends at a constant percentage per year. Joinpoint software (Joinpoint Command Line Version 4.9.1.0), developed by the United States National Cancer Institute Surveillance Research Programme, was used[25].

Results

The analysis included data from 19 countries each with 30 years of data. Over the observation period, significant changes were observed in the burden of disease across all 19 countries. ASMR, ASIR and DALYs per 100 000 and MII per country between 1990 and 2019 for males and females are displayed in Appendix A, Supplemental Digital Content 2, http://links.lww.com/JS9/A585. Appendix B, Supplemental Digital Content 2, http://links.lww.com/JS9/A585 demonstrates sex-specific Joinpoint regression analyses for appendicitis ASMRs, ASIRs, MIIs and DALYs between 1990 and 2019.

Mortality

Overall, all 19 nations demonstrated a decrease in ASMR in females and males (Appendix C.1, Supplemental Digital Content 2, http://links.lww.com/JS9/A585), with increases in ASMR noted in certain countries among males and females in the late 1990s/early 2000s (Canada, Denmark, Greece, Ireland, Netherlands, Spain, Sweden, UK, USA). In 2019, the median ASMRs across EU15+ nations were 0.08/100 000 and 0.13/100 000 for females and males, respectively, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. Among females, the highest ASMRs in 2019 were observed in Denmark, the UK and the Netherlands (0.17/100 000, 0.13/100 000 and 0.10/100 000, respectively), and the lowest in Italy, Ireland and Austria (0.04/100 000, 0.05-/100 000 and 0.05/100 000, respectively). Among males, the highest ASMRs in 2019 were observed in Denmark, the UK and Germany (0.29/100 000, 0.17/100 000 and 0.17/100 000, respectively), and the lowest ASMRs in Greece, Ireland and Italy (0.07/100 000, 0.07/100 000 and 0.08/100 000, respectively). The median change in ASMR for females between 1990 and 2019 was −0.06/100 000 (median percentage change of −52.12%) and −0.12/100 000 in males (median percentage change of −53.18%). The greatest overall reduction in ASMR was observed in Finland for females (−77.96%) and Germany for males (−66.29%), with the smallest proportional decreases in the UK (−13.82%) and the USA (−21.33%) for females and males, respectively. Final positive trends were observed in three countries for females (Canada, Greece, the UK) and 5 countries for males (Denmark, Finland, Greece, UK, USA) representing an increase in appendicitis ASMR over the most recent subsection of the observation period analysed (2015–2019 for most countries).

Incidence

Overall, most trends observed for males and females were relatively static with both positive and negative trends occurring during the observation period (Appendix C.2, Supplemental Digital Content 2, http://links.lww.com/JS9/A585). In 2019, the median ASIRs across EU15+ nations were 251/100 000 and 278/100 000 for females and males, respectively. In 2019, the highest ASIRs among females were observed in Austria, Germany and Sweden (470-/100 000, 394/100 000 and 360/100 000, respectively), and the lowest in the USA, Portugal and Canada (153/100 000, 160-/100 000 and 168/100 000, respectively). For males, the highest ASIRs in 2019 were observed in Austria, Germany and Sweden (409/100 000, 382/100 000 and 361/100 000, respectively), and the lowest in the USA, Canada and Portugal (169/100 00, 186-/100 000 and 196/100 000, respectively). Over the period in question, the median change in ASIR for females was +16.80/100 000 (median percentage change +7.22%) and +10.31/100,000 for males (median percentage change +3.78%). The greatest reduction in ASIR between 1990 and 2019 was observed in the USA for both females (−12.95%) and males (−10.24%). Overall, 4 out of the 19 nations demonstrated a decrease in ASIR in females over the 30-year study period, compared with and 2 out of 19 countries in males. The subsection of the observation period covered by the most recent trends (approximately in the years 2012–2019) demonstrated decreasing ASIR trends in 8 countries for females (Australia, Austria, Belgium, Canada, Denmark, Italy, Luxembourg, Sweden) and 11 countries for males (Austria, Belgium, Canada, Denmark, Finland, France, Ireland, Italy, Luxembourg, Spain, Sweden).

Mortality to incidence index

All 19 nations demonstrated a decrease in MII in both females and males over the observation period (Appendix C.3, Supplemental Digital Content 2, http://links.lww.com/JS9/A585). In 2019, the median MIIs across EU15 + nations were 0.27 and 0.44 for females and males, respectively. In 2019, the highest MIIs among females were observed in the UK, Denmark and the USA (0.68, 0.66 and 0.60, respectively), and the lowest in Austria, Italy and Ireland (0.10, 0.19, and 0.20, respectively). For males, the highest MIIs in 2019 were observed in Denmark, the USA and Portugal (1.02, 0.94 and 0.83, respectively), and the lowest in Austria, Ireland and Greece (0.23, 0.27 and 0.27, respectively). Over the period in question, the median change in MII for females was – 0.29 (median percentage change of – 56.52%) and – 0.45 for males (median percentage change of – 55.74%). The greatest reduction in MII between 1990 and 2019 was observed in Finland for females (– 76.24%) and Germany for males (– 72.15%). The subsection of the observation period covered by the most recent trends (~2015–2019) demonstrated increasing case fatality in four countries in females (Belgium, Denmark, Greece, Luxembourg) and eight countries in males (Belgium, Denmark, Finland, Italy, Luxembourg, Netherlands, UK, USA).

Disability-adjusted life-years

Overall, all 19 nations demonstrated a decrease in DALYs in females and males over the observation period (Appendix C.4, Supplemental Digital Content 2, http://links.lww.com/JS9/A585). In 2019, the median DALYs across EU15 + nations were 4.60/100 000 and 6.08/100 000 for females and males, respectively. In 2019, the highest DALYs among females were observed in Austria, Denmark and Germany (6.53/100 000, 6.20/100 000 and 6.12/100 000, respectively), and the lowest among in Italy, Portugal and Ireland (3.55/100 000, 3.69/100 000, and 3.91-/100 000, respectively). For males, the highest DALYs in 2019 were observed in Denmark, Germany and Austria (8.89/100 000, 7.83/100 000 and 6.76/100 000, respectively), and the lowest in Italy, Ireland and Greece (4.45/100 000, 4.58/100 000 and 4.73/100 000, respectively). Over the period in question, the median change in DALYs for females was – 1.47/100 000 with a median percentage change of – 23.57%. For males, the median change in DALYs was – 3.05/100 000 with a median percentage change of – 33.81%. The greatest reduction in DALYs between 1990 and 2019 was observed in Finland for females (– 52.19%) and in Germany for males (– 45.81%), Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Discussion

In this observational analysis of EU15 + appendicitis trends over a 30-year study period, an overall decrease in ASMR was noted in all 19 countries for both males and females. Yet, in contrast to the overall trends, increases in ASMR were noted in several countries among males and females in the late 1990s/early 2000s (Canada, Denmark, Greece, Ireland, Netherlands, Spain, Sweden, UK, USA) with subsequent decreases thereafter. By contrast, ASIR trends were flatter throughout the observation period with a tendency towards marginal increases in ASIRs observed in most countries. There was, however, an observable increase in ASIR during the 1990s/early 2000s in several EU15 + nations for both sexes, with an apparent predilection for Northern European nations (Austria, Belgium, Denmark, Germany, Italy, Luxembourg, Norway, Sweden) , Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

More broadly, males suffered poorer disease outcomes than female patients with most countries reporting worse outcomes in all years of the observation period with regards to ASMR (19/19, 100% of countries), MII (18/19, 94.7% of countries) and DALYs (18/19, 94.7% of countries). Exceptions include Austria (DALYs higher in females 2009–2012) and Norway (MII higher in females 2014–2019). There was less of a sex disparity among ASIRs, with higher rates reported among females for more than half of the years in the observation period in 5/18 countries (Austria, Germany, Italy, Luxembourg, Sweden). These trends are in keeping with mortality and incidence data from the wider literature[6,26]. Explanations are likely multifactorial but the trends may partially be accounted for by an increased risk of appendiceal perforation among males[27]. However, substantial data explaining the sex differences observed are lacking in the literature and represent an avenue for future investigation.

The data demonstrate a shifting burden of appendicitis across the EU15 + nations, with decreasing mortality despite increasing incidence rates, and it is likely that a complex interaction of multiple factors contributes to the changing landscape observed in this analysis, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. Of direct relevance is the current debate surrounding operative versus non-operative management in uncomplicated appendicitis. Greater adoption of antibiotic therapy as the mainstay in the management of uncomplicated appendicitis since the 2000s may correlate not only with the reduction in ASMR, MII and DALYs across many of the EU15 + nations but also with the subtle increase in ASIR noted. While a substantial body of evidence supports the notion that antibiotics are largely effective in the management of uncomplicated appendicitis[11–14,28,29], there is also a risk of treatment failure: 46.4% of recurrence at 1 year in one study, 29% appendicectomy rate by 90 days in another[30,31]. In essence, while antimicrobial management of uncomplicated disease may be effective in preventing appendicectomy and its associated risk profile in up to 72.6% of cases, it remains to be seen whether outcomes data support its validity as a suitable solution based on rates of longer-term recurrence. Hence, further studies investigating longer-term outcomes are necessary, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Also pertaining to antibiotic therapy, it must be acknowledged that local protocol variance may account for difficulties in the optimal application of a non-operative management approach. For instance, a recent national survey conducted in Norway and Sweden reported variable adoption of antibiotic treatment for uncomplicated appendicitis, citing a lack of formal clinical guidelines on the matter as a contributing factor[32] to the relatively higher ASMRs and ASIRs seen in certain countries. This is a somewhat paradoxical finding in two Scandinavian countries given that a substantial proportion of the discourse validating non-operative management is generated within Northern Europe[12,13,28,29] which, as a result, may be expected to have clearer guidance on the use of specific antimicrobials.

A second possible contributing factor to the overall decline in ASMR, MII and DALYs during the observation period might be the more widespread adoption of computed tomography (CT)

imaging as the gold-standard diagnostic test for appendicitis since the 1990s. With high levels of accuracy and availability coupled with ease of interpretation[33], this development may have contributed to the reduction in disease burden across EU15 + nations through its ability to optimise management by differentiating between uncomplicated and complicated appendicitis, while preventing false negative appendicectomies[34], Supplemental Digital Content 3, http://links.lww.com/JS9/A589.One particularly relevant case study would be the USA. One of very few EU15 + countries to boast a decreasing ASIR in both females and males, conversely the USA suffered the smallest percentage decrease in case fatality (MII) in both sexes over the observation period combined with the second highest case fatality among males and the third highest case fatality among females (both in 2019) , Supplemental Digital Content 3, http://links.lww.com/JS9/A589. This occurs on a backdrop of increasing ASMR and MII among males in the final years of the observation period. The explanation behind these observations is likely complex and multifactorial, but it is possible that clinical guidelines shed some light on the situation. In the 2010 guidelines published by the Surgical Infection Society and the Infectious Diseases Society of America on the diagnosis and management of intra-abdominal infections[35], CT imaging is the diagnostic modality of choice with acknowledgement of ultrasound scanning being a notable omission. This correlates with international guidance at the time[36]. Contrastingly, updated international guidelines from the World Society of Emergency Surgeons[2] now places substantial emphasis on both risk stratification and the appropriate application of ultrasound diagnostic techniques, perhaps reflecting recent failings in practice or an over-reliance on CT imaging contributing to suboptimal patient outcomes.

Changes to surgical practice must also be acknowledged. Crucially, more widespread adoption of laparoscopic appendicectomy during the 1990s may contribute to the decline in ASMR, MII and DALYs over the next decade. First performed in 1983 by Semm[37], laparoscopic appendicectomy has been associated with shorter inpatient stay, reduced perioperative pain, low wound infection risk and comparable rates of other complications, albeit with a slightly increased risk of intra-abdominal abscess, intraoperative bleeding and urinary tract infection when compared with open appendicectomy[38]. The adoption of this new technique may account for the persistence of adverse outcomes in ASMR, MII and DALYs in certain EU15 + countries (Denmark, Germany) in the early years of the observation period while laparoscopic appendicectomy remained in its infancy. Also significant is the way in which prophylactic appendicectomy has fallen out of routine clinical practice, potentially reducing the degree of mortality and morbidity relating to surgical complications[39], Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Finally, differing forms of appendicitis may contribute to the shifting temporal trends observed. Recent epidemiological data have made a distinction between the perforating and non-perforating forms of the disease, specifically that perforating appendicitis steadily increased in the early years of the observation period while non-perforating appendicitis initially decreased before beginning to trend upwards[40]. Further analysis is required to characterise these secular trends to determine whether changes to the proportions of perforating and non-perforating appendicitis may have a bearing on the increasing ASMRs and MIIs observed in the latter years of the observation period, or whether less substantiated factors may be responsible.

Strengths and limitations

The strengths of this analysis relate primarily to the nature of the data, specifically the large number of countries included and the duration of the observation period which demonstrate long-term temporal trends at a population level. The standardised estimates used facilitate direct comparison between countries and the originality of the analysis (being the first study to use GBD data with a focus on appendicitis in EU15 + nations) provide high-level insights for key stakeholders, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. The limitations, which are applicable to all GBD analyses and common to observational studies, include an inability to establish causal inferences and a dependence on the quality of input data. This issue arises from the probable existence of multiple confounding factors caused by national variations in medical practice and data recording, particularly with regards to death incidence data. However, this is somewhat mitigated by the relatively higher quality of EU15 + civil registration and vital statistics data[41] and corrections for garbage codes made during the GBD data analysis process, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Conclusions

Overall reductions in appendicitis ASMRs, MIIs and DALYs between 1990 and 2019 in EU15 + nations can be observed among males and females, Supplemental Digital Content 3, http://links.lww.com/JS9/A589. Contrastingly, ASIRs have remained stable throughout the observation period. Variations in both diagnostic and management strategies for appendicitis over the study period are likely contributory to the changing trends. This study highlights the importance of continued clinical and financial efforts to optimise the management of appendicitis and, in doing so, reduce the burden of the disease across EU15 + nations, Supplemental Digital Content 3, http://links.lww.com/JS9/A589.

Ethical approval

Not applicable. No involvement of human subjects. Anonymised publicly accessible population level estimate data used for analysis.

Source of funding

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Author contribution

D.W.P. and J.S. conceived the study and were responsible for its design. Statistical analysis was performed by K.B. Interpretation of results and drafting of the manuscript was performed by all authors. All authors read and approved the final manuscript.

Conflicts of interest disclsoure

There are no conflicts of interest.

Guarantor

Mr Joseph Shalhoub.

Data statement

All data are publicly available via the GBD Results Tool - http://ghdx.healthdata.org/gbd-results-tool.

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