

SUPPLEMENTARY MATERIALS

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S1. Number of potential and actual Live births (LBs) of children with Down syndrome (DS)

S1A. Estimates of nonselective LBs of children with DS

The number of children with DS that would have been born in absence of elective terminations can be estimated on the basis of maternal age. Morris et al. developed a model of maternal-age specific chances for a LB of a child with DS.¹ We applied this model to data on maternal age distribution, as derived from national statistical offices, and the Demographic Yearbook Collection of the United Nations (for details on the sources, see S1B).²

For older years, maternal ages were not available in single years, but only in 5-year maternal age-groups. Earlier, de Graaf et al. constructed 5-year maternal age-specific chances on basis of U.S. birth data with single-year maternal age bands, available for 1931–1937 and from 1946 onwards in the Vital Statistics of the United States (<https://www.cdc.gov/nchs/products/vsus.htm>).^{3,4} For 1938–1945, interpolation was applied. The 5-year maternal age chances evolve slightly over the years (as the maternal age distribution within these 5-year bands changes over time). We have assumed that this would apply to the Australian and New Zealand samples, too. The use of these constructed 5-year maternal age-specific chances by year of birth is fine-tuning with only slight effects on the results.

Australia

Data on births in the general population by maternal age in single-year maternal age bands were available from the Australian Bureau of Statistics (ABS) for 1975–2019 (see S1B for sources). For 1936–1974, the Demographic Yearbook Collection of the United Nations (DYB) provides these data in 5-year maternal age bands. For 1907–1915 and 1917–1935, these data were available in the Year Book Australia 1909–1936 of the ABS. Nonselective prevalence for 1916 was interpolated. Nonselective prevalence for 1900–1906 was assumed to be similar to that in 1907. From 1901 onwards, the total number of LBs in the general population is reported in the Year Book Australia. For 1900, we found information on a Wikipedia page on demographics in Australia (see S1B).

Aboriginal people

Before 1967, births of Aboriginal people were not included in the data of ABS or DYB. In the Year Book Australia 2001, Graeme Hugo (see S1B) presents some data on Aboriginal peoples from historical censuses. Before 1967, the Aboriginal population was around 1% or less of the Australian population. As there are uncertainties (we have no information on historical maternal age distribution, for instance) and the effect on the estimates of the population of people with DS in Australia would be very small, we have decided not to correct for the exclusion of Aboriginal people from the data prior to 1967.

New Zealand

Data on births in the general population by maternal age in single-year maternal age bands were available from Stats NZ for 1962–2020 (see S1B for sources). For 1936–1941 and 1943–1961, the Demographic Yearbook Collection of the United Nations (DYB) provides these data in 5-year maternal age bands. Nonselective prevalence for 1942 was interpolated. For 1912–1918 and 1920–1935, the relevant data were available in the Yearbook collection 1910–1936 of Stats NZ. Nonselective prevalence for the year 1919 was interpolated; for 1900–1911, it was assumed to be similar to that in 1912. Total number of births in the general population was available for 1900–1935 in the Yearbook collection.

Maori

Before 1962, births of Maori were not included in the maternal age distribution data of Stats NZ or DYB. However in the Yearbook collection of Stats NZ, the total annual number of Maori births is reported from 1914 onwards. We have assumed that, before 1914, the percentage of Maori births in total births was similar to that in 1914–1916. Census data show that the percentage of Maori in the general population was more or less constant between 1901–1936, at around 5%.

In addition, we have data on the Maori age-specific fertility, and the Maori female age-distribution in the 1960s. On the basis of these data, the number of births by 5-year maternal bands can be constructed, and so nonselective prevalence of DS in Maori can be estimated. For the 1960s, these estimates for Maori and for European NZ population are highly similar. We have assumed that before the 1960s, nonselective LB prevalence for DS in Maoris was similar to that in European NZ population, too. For 1900–1961, we have corrected the total number of births in the general population, and our estimate of the number of LBs of DS, accordingly.

S1B. Sources for number of LBs by maternal age in the general population

Australia

Years: 1975-2019

Source: Dataset - Births, by nuptiality, by age of mother.

Australian Bureau of Statistics (ABS)

https://stat.data.abs.gov.au/Index.aspx?DataSetCode=BIRTHS_AGE_MOTHER

Data extracted on 17 June 2021 from ABS.Stat, Commonwealth of Australia.

(Maternal age in single years)

Years: 1936-1974

Source: DYB (Demographic Yearbook Collection of the United Nations)

<https://unstats.un.org/unsd/demographic-social/products/dyb/>

(Maternal age in 5 year groups)

Years: 1900-1935

Source: Year Book Australia 1909-1936

Australian Bureau of Statistics (ABS)

<https://www.abs.gov.au/AUSSTATS/abs@.nsf/second+level+view?ReadForm&prodno=1301.0&viewtitle=Year%20Book%20Australia~2012~Latest~24/05/2012&&tabname=Past%20Future%20Issues&prodno=1301.0&issue=2012&num=&view=&>

(Maternal age in 5 year groups available for 1907-1915 and 1916-1935; Total number of LBs for 1901-1935; non-selective prevalence for 1916 was interpolated; non-selective prevalence for 1900-1906 was assumed to be similar to that in 1907)

Total number of LBs in 1900 derived from:

https://en.wikipedia.org/wiki/Demography_of_Australia#Vital_statistics_since_1900 which refers to "Developed countries database".

https://www.ined.fr/en/everything_about_population/data/online-databases/developed-countries-data-base/)

Information on the Aborigines population in Australia.

Source: Hugo, G. (2001). A century of population change in Australia. In: Year Book Australia, 2001.

<https://www.abs.gov.au/ausstats/abs@.nsf/featurearticlesbyreleasedate/0b82c2f2654c3694ca2569de002139d9?opendocument>

New Zealand

Years: 1962-2019

Source: Stats NZ

Dataset Live Births by Age of Mother

<http://infoshare.stats.govt.nz/Default.aspx>

(Based on/includes Stats NZ's data which are licensed by Stats NZ for reuse under the Creative Commons Attribution 4.0 International licence.)

Retrieved 17 June 2021

(Maternal age in single years)

Years: 1936-1961

Source: DYB (Demographic Yearbook Collection of the United Nations)

<https://unstats.un.org/unsd/demographic-social/products/dyb/>

(Maternal age in 5 year groups; no data available on maternal age for the year 1942; nonselective prevalence for 1942 was interpolated. Total number of births available for 1936-1961. Maori not included in the data)

Years: 1900-1935

Source: Stats NZ

Yearbook collection: 1910–1936

<https://www.stats.govt.nz/indicators-and-snapshots/digitised-collections/yearbook-collection-18932012/>

(Maternal age in 5 year groups available for 1912-1918 and 1920-1935. Total number of births available for 1900-1935. Nonselective prevalence for the year 1919 was interpolated; non-selective prevalence for 1900-1911 was assumed to be similar to that in 1912; Maori not included in the data on maternal age distribution)

Information on the total number of Maori births 1914-1962 from:

Yearbook collection: 1910–1964

<https://www.stats.govt.nz/indicators-and-snapshots/digitised-collections/yearbook-collection-18932012/>

Information on the age distribution of the female Maori population for 1961, 1963, 1964, 1966, 1968, 1969, from:

Stats NZ

Yearbook collection: 1964-1971

<https://www.stats.govt.nz/indicators-and-snapshots/digitised-collections/yearbook-collection-18932012/>

Information on age-specific fertility of Maori, for 1962 onwards, from:

Stats NZ

Dataset Age-specific fertility rates by 5 year age group (Maori and total population) (Annual-Dec)

<http://infoshare.stats.govt.nz/Default.aspx>

(Based on/includes Stats NZ's data which are licensed by Stats NZ for reuse under the Creative Commons Attribution 4.0 International licence.)

Retrieved 17 June 2021

Information on the size of the Maori population in 1901, 1906, 1911, 1916, 1921, 1926, 1936, from: Stats NZ

Yearbook collection, 1940

<https://www.stats.govt.nz/indicators-and-snapshots/digitised-collections/yearbook-collection-18932012/>

S1C. Estimates of actual LBs of children with DS

Australia

Prenatal diagnostics were not available before 1967 in any country; as such, the effect of prenatal diagnostics on the LB prevalence of DS will have been zero. For these early years, we have used the estimates of nonselective prevalence as the best approximation of DS LB prevalence.

For 1965–1970, the reduction in LBs of children with DS resulting from elective terminations, will be very low. De Graaf et al. have estimated this to be less than 1% in the period 1965–1970 for the U.S.³; de Graaf et al. have modeled similarly for Europe.⁴ We do the same for Australia.

Data on actual LBs of children with DS in Australia born in the 1970s are scarce. Staples et al. report data on births and terminations from 1960 to 1989 for Southern Australia.⁵ The authors estimate total DS prevalence by adding 70% of the DS-related elective terminations to the number of births of children with DS. As they also report live births in the general population by maternal age, we could estimate the nonselective prevalence for each period of 5-years reported. With the exception of 1960–1964, the total DS prevalence as estimated by Staples et al. is only slightly lower than our estimates of nonselective prevalence (on average, 5% less for the period 1965–1989), which suggests a high level of reporting in the study of Staples et al.⁵ Before 1975, no elective terminations were reported. For 1975–79, Staples et al. found 5 elective terminations and 84 births of children with DS, suggesting a reduction percentage of 4% (correcting for natural loss/miscarriage that would have occurred absent termination). For Western Australia, for the period 1966–1975, Mulcahy reports 231 LBs of children with DS and 4 elective terminations, which confirms that reduction percentage before 1975 was low.⁶ Hui et al. report 7 prenatal DS diagnoses in Victoria between 1975–1979.⁷ In this period, absent elective terminations, 363 LBs would have been expected on the basis of maternal age distribution in Victoria. So it appears that the effect of prenatal diagnoses and elective terminations was very small before 1980.

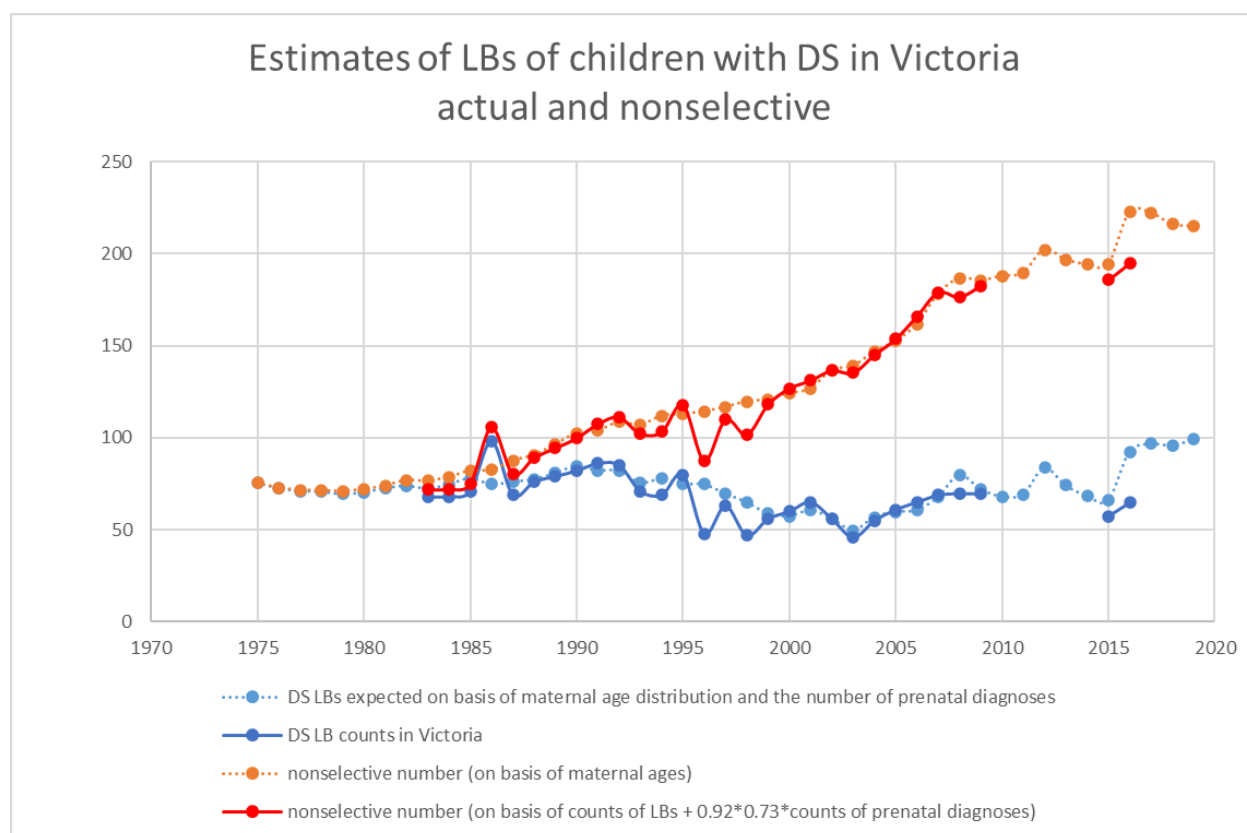
Lancaster & Pedisich report for Australia countrywide 251 LBs of children with DS in 1982.⁸ For this year, our estimate of the number of nonselective births is 300, which implies a reduction of 15%. For modeling, we have assumed that reduction was zero in 1967, 1% in 1972, 4% in 1977, and 15% for 1982. Values in between were interpolated.

For 1982–2003, the National Perinatal Statistics Unit (see S1D) reported the number of LBs of children with DS in Australia, countrywide. For some of the years, there are small numbers of births in which the pregnancy outcome (SB or LB) was not specified. We have distributed these cases over the categories of SB and LB in a similar manner to the cases with a known outcome. For 1998–2003, data from the Northern Territory (NT) are missing. We have assumed that the prevalence in NT was similar to the estimate for the rest of Australia.

In addition, we found data for NSW (1990–2018), Queensland (1981–1983; 1988–2004; 2008–2020), South Australia (SA) (1980–1998; 2002–2011; 2013–2017), Victoria (1983–2010; 2013–2016), and West Australia (WA) (1980–2014). The values for Victoria in the years 2013–2014 appear to be outliers, and the report “Congenital anomalies in Victoria 2013–2014” stated that there was considerable underreporting in these years. We left out the Victorian data on LBs of children with DS for these two years.

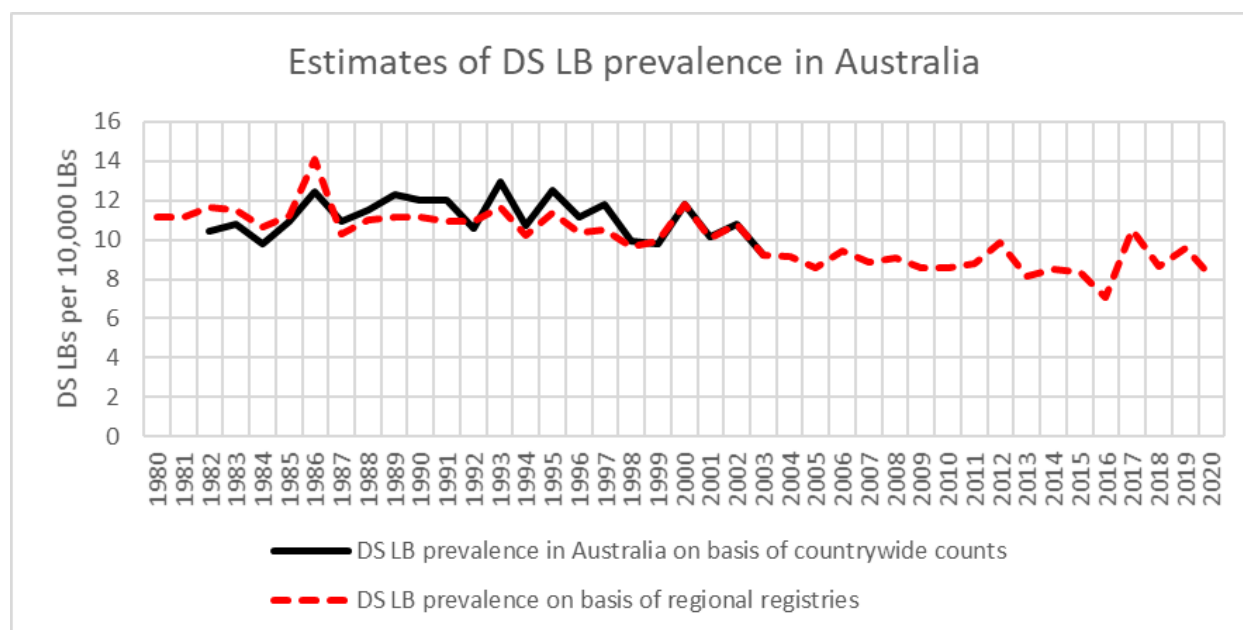
For 2015–2016, the information in the report “Congenital anomalies in Victoria 2015–2016” is incomplete in regards to the prenatal or postnatal status of the cases and the outcomes of pregnancies. In Hui et al. (2020), additional information on prenatal or postnatal status for this period of time could be found.⁹ We have assumed that of the postnatal diagnoses, 5% were either a miscarriage or stillbirth and, of the prenatal diagnoses, 0.08×0.73 or 5.8% were LBs, assuming that, with a prenatal DS diagnosis, 8% of the expectant couples choose to carry the pregnancy to term, of which 27% ends in natural loss or SB.

Interestingly, Hui et al. (2015) published a study with full data on the annual number of prenatal DS diagnoses in Victoria from 1976 to 2013⁷, and Pynaker et al. (2020) reported full data on prenatal DS diagnoses in Victoria from 2013 to 2020.¹⁰ Earlier, Collins et al. found that between 1986–2004 only 5.3% of the pregnancies in Victoria with a prenatal diagnosis of DS were LBs. That is highly similar to our estimate of 0.08×0.73 (5.8%).¹¹ For the period 1976–2019, we assume that a similar 92% of the prenatal diagnoses of DS were terminated and that natural loss would have been 27% in absence of elective terminations.¹¹ So for every 100 prenatal diagnoses, there would be $100 \times 92\% \times 73\% = 67$ fewer children with DS born. If we subtract these estimates from our estimates of nonselective annual numbers of LBs of children with DS on the basis of maternal age distribution in Victoria, we can derive the number of expected LBs. These estimates appear to be highly similar to the counts of LBs in Victoria as reported in the Victorian Congenital anomalies reports (see S1D). In addition, the estimates of nonselective numbers on the basis of maternal ages are highly similar to estimates based on the counts of LBs + $(0.92 \times 0.73 \times \text{number of prenatal diagnoses})$, implying that there is little or no underascertainment of cases in the surveillance program (see the graph below). However, for the years 2016–2019, there seems to be some anomaly. The number of potential LBs (on the basis of maternal ages) increases from 194 in 2015 to on average 219 in 2016–2019, but the number of prenatal DS diagnoses (as reported in Pynaker et al.) decreases from 204 in 2015 to on average 179 in 2016–2019.¹⁰ A possible explanation might be that some expectant parents decided to terminate their pregnancy on the basis of a positive NIPT result only, perhaps in combination with results from an echo, without seeking confirmation by CVS or amniocentesis. The number of NIPT tests has clearly risen in recent years, so if this is an effect, it will only have a real influence in recent years. As we feel uncertain about the estimates for 2016–2019 on basis of the number of prenatal diagnoses, we have excluded these from our modeling.



For the years 1980–1982 and 2010–2014, for Victoria, we have used our estimates of LBs of children with DS as expected on the basis of maternal age and number of prenatal diagnoses, under the assumptions mentioned above. For 1983–2009 and 2015–2016, we have used the LB counts by the surveillance program.

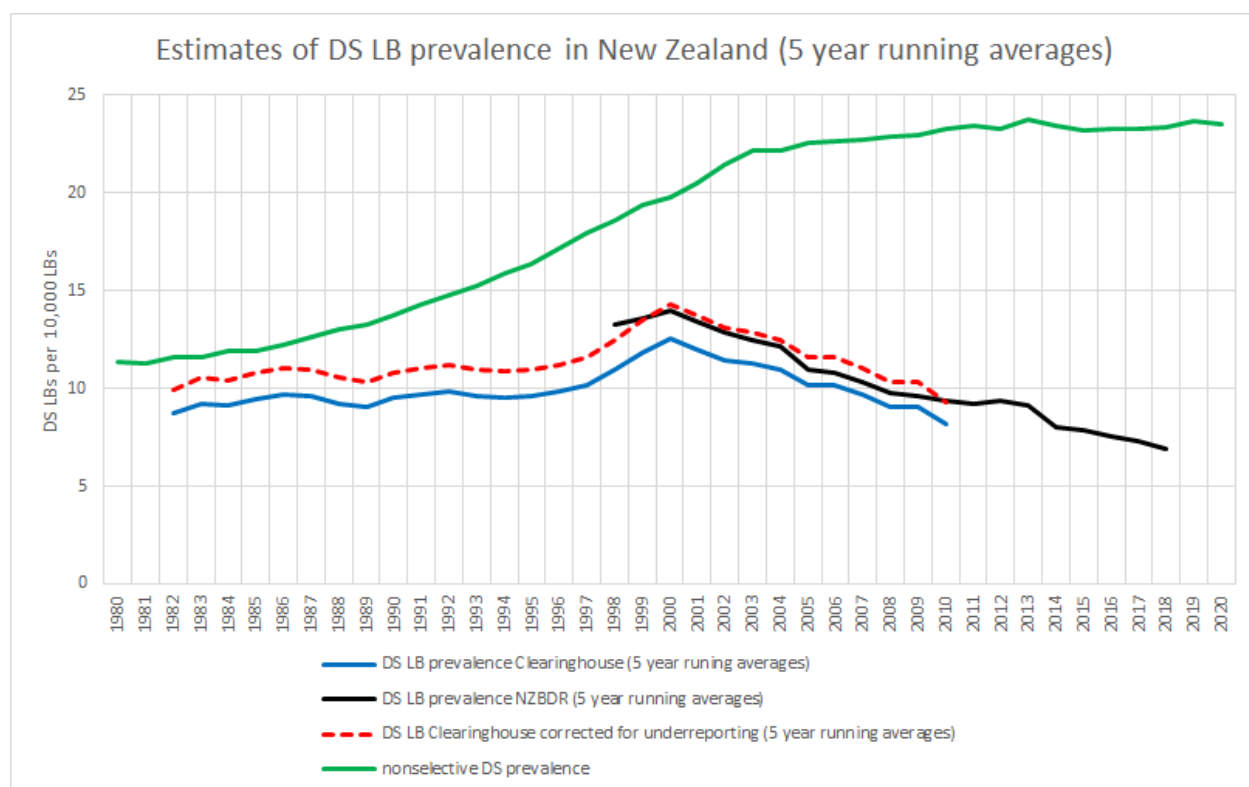
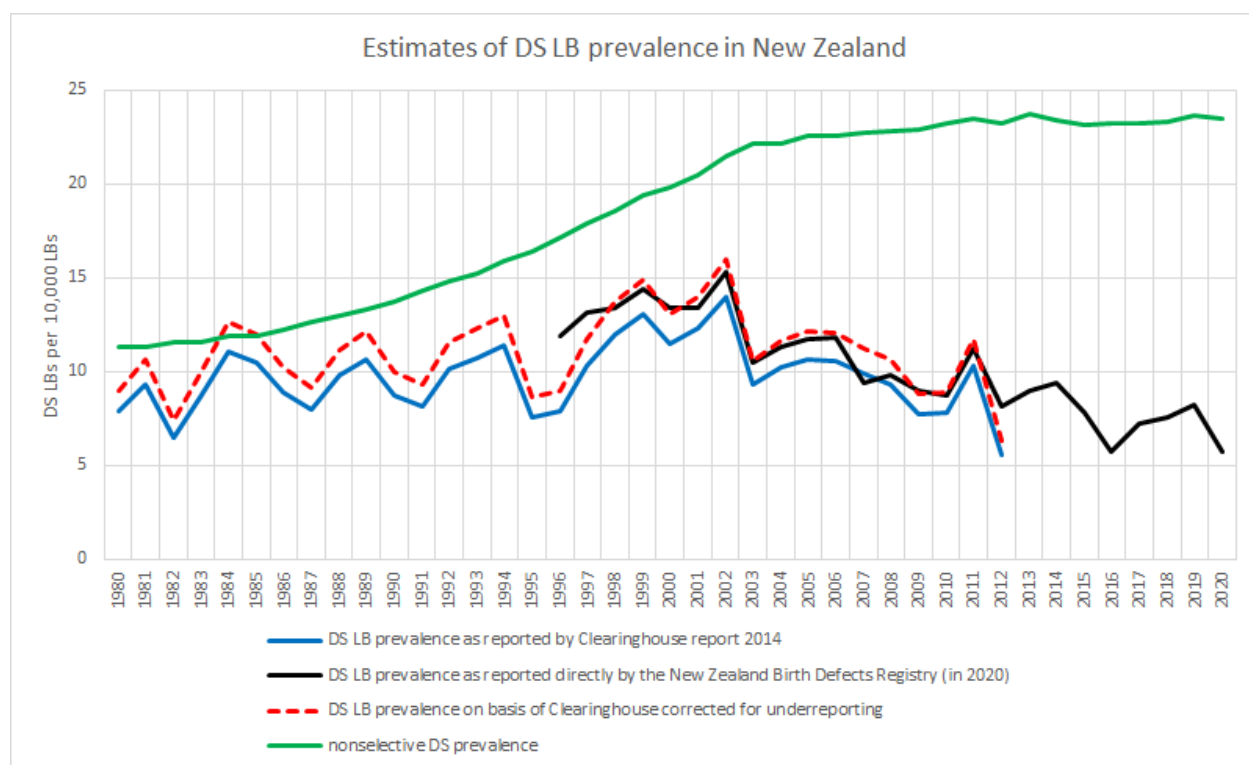
For 1980–2020, the regional data for all 5 states cover on average 76% of the general births in Australia, with 53% for 1980–1984, 50% for 1985–1989, 94% for 1990–1994, 93% for 1995–99, 92% for 2000–2004, 83% for 2005–2009, 94% for 2010–2014, 69% for 2015–2018, and 20% for 2019–2020. For the overlapping years, 1982–2003, estimates on the basis of the data countrywide and on the basis of the regional registries are fairly similar. See the graph below in which estimates of annual numbers are used, and not 5-year running averages.



For further modeling the actual DS LB prevalence for 1982–2003, we have used the estimates on the basis of the countrywide data of the National Perinatal Statistics Unit. From 2004–2018, in order to reduce the possible random fluctuation in regional samples, we used 5-year running averages based on the regional data combined (the sum of all registered LBs with DS divided by the sum of all LBs in the regions with data, multiplied by 10,000). For 2019, we used the 3-year average of 2018–2020. For 2020, we have used the average of 2019–2020.

New Zealand

The Clearinghouse Report (2014) reports data on LBs with DS in New Zealand for 1980–1992 and 1994–2012. We interpolated the value for 1993. Professor Barry Borman of the New Zealand Birth Defects Registry (NZBDR) provided data for 1996–2020 by personal email. For the overlapping years (1996–2012), there seems to be an underreporting in the Clearinghouse Report. The NZBDR data were on average 14% higher. We have assumed a similar extent of underreporting for 1980–1995 and have corrected accordingly. The raw data and corrected data are presented in the two figures below. In our modelling we have used the data provided by Prof. Barry Borman for 1996 onwards. For 1980–1995, we used the Clearinghouse data, corrected for underreporting.



Before 1980, we lack data for New Zealand. For the period 1980–1984, the reduction (on the basis of the data in the graphs above) was estimated at 14%, very similar to the estimate for Australia for the same period. For modeling, we have assumed that reduction was 0% in 1967, 1% in 1972, 4% in 1977 (like we estimated for Australia), and 14% for 1982. Values in between were interpolated.

S1D. Sources of actual LBs of children with DS

Australia

Countrywide

Years 1982-1992

Source: Lancaster & Pedisich (1995). Congenital Malformations Australia, 1981-1992. Australian Institute of Health and Welfare. National Perinatal Statistics Unit. Sydney, 1995

Years 1985-1994

Source: Lancaster et al. (1997). Congenital Malformations Australia, 1993 and 1994. Australian Institute of Health and Welfare. National Perinatal Statistics Unit. Sydney, 1997.

Years 1987-1996

Source: Hurst et al. (1999). Congenital Malformations Australia, 1995 and 1996. Australian Institute of Health and Welfare. National Perinatal Statistics Unit. Sydney, 1999.

For 1986-1996, there are some cases with missing outcomes reported, which could be LB or SB. We have distributed these as we had done so with the known cases

Years 1997

Source: 'Congenital Malformations Australia 1997' is available electronically only from the Australian Institute of Health and Welfare. National Perinatal Statistics Unit based at the University of New South Wales.

[https://www.aihw.gov.au/reports/mothers-babies/congenital-malformations-australia-1997/report-editi-
ons](https://www.aihw.gov.au/reports/mothers-babies/congenital-malformations-australia-1997/report-editi-
ons)

For 1997, only the total number was available, including LBs and SBs (gestation ≥ 20 weeks; birth weight ≥ 400 g; late TOPs included). However for 1996, LBs were 90.4% of this total, and for 1998 it was 87.5%. We assumed the average of 88.9% for 1997.

Years 1998-2001.

Source: Abeywardani et al. (2007). Congenital Malformations Australia, 1998-2001. Australian Institute of Health and Welfare. National Perinatal Statistics Unit. Sydney, 2007.

Years 2002-2003.

Source: Abeywardani & Sullivan. (2008). Congenital Malformations Australia, 2002-2003. Australian Institute of Health and Welfare. National Perinatal Statistics Unit. Sydney, 2008.

New South Wales

Years: 1990-1995

Source: Public Health Division. New South Wales Mothers And Babies 1996. Sydney: NSW Department of

Health, 1998.

Years 1996-1999

Source: Public Health Division. New South Wales Mothers and Babies 2000. Sydney: NSW Department of Health, 2001.

Years: 1999-2004

Source: Centre for Epidemiology and Research. NSW Department of Health. New South Wales Mothers and Babies 2005. NSW Public Health Bull 2007; 18(S-1).

Years: 2004-2009

Source: Centre for Epidemiology and Evidence. New South Wales Mothers and Babies 2010. Sydney: NSW Ministry of Health, 2012.

Years: 2007-2016

Source: Congenital Conditions, NSW 2007 to 2016. Table 10: Cases with selected congenital conditions by pregnancy outcome. NSW 2007 to 2016 HealthStats NSW. NSW Government. Provided on request.

Year 2017-2018

Source: Source: Table 1: Down syndrome, NSW 2017 to 2018. Register of Congenital Conditions, Secure Analytics for Population Health Research and Intelligence, NSW Ministry of Health. Provided on request.

Queensland

Years: 1981-1983

Source: Bell J. et al. (1986). The impact of prenatal diagnosis on the occurrence of chromosome abnormalities. Prenat Diagn. Jan-Feb 1986;6(1):1-11. doi: 10.1002/pd.1970060102.

Years: 1988-2004

Source: Roselli T. (2006). Summary statistics on congenital anomalies in Queensland 1988-2004. Epidemiology Services Unit, Health Information Centre, Reform & Developmental Division. Queensland Health.

Before 2007, the Queensland Perinatal Data Collection (QPDC) did not include information on terminations of pregnancy before 20 weeks. The data for 1988-2004 contain SBs (including late terminations). In Australia as a whole, for the period 1988-2003 (see the earlier info on Australia country wise), 92% in 1988 to 88% in 2003 of the total of LBs and SBs (including late TOPs) were LBs. We assumed the same for Queensland.

Years: 2007-2010

Source: Howell S, Endo T, MacLeod S, Cornes S (2011). Congenital Anomalies in Queensland: 1 July 2007 to 30 June 2010 Health Statistics Centre, Queensland Health. Statistical Analysis Report #1 September 2011.

Years: 2011-2020

Source: Cases of Downs Syndrome, by Statistical Area Level 4 (SA4) and all Queensland, 2011 to 2020p. Congenital Anomaly Linked File (CALF) and Queensland Perinatal Data Collection (PDC), Statistical Services Branch, Queensland Department of Health. Date of extraction: 11/10/2021. Prepared by:

Statistical Analysis and Linkage Unit, Statistical Services Branch (ph: 07 3708 5710). SSB request No: 33450.

South Australia

Years: 1960-89

Source: Staples J, Sutherland GR, Haan EA & Clisby S (1991). Epidemiology of Down Syndrome in South Australia, 1960-89. Am. J. Hum. Genet. 49:1014-1024

Years: 1982-1998

Cheffins T. et al. (2000). The impact of maternal serum screening on the birth prevalence of Down's syndrome and the use of amniocentesis and chorionic villus sampling in South Australia. BJOG 107 (12):1453 – 1459.

Years: 2002

2002 Annual Report of The South Australian Birth Defects Register.

Years: 2003

2003 Annual Report of The South Australian Birth Defects Register.

Years: 2004

2004 Annual Report of The South Australian Birth Defects Register.

Years: 2005

Source: van Essen P, Gibson C, Scott H, Willoughby C, Chan A, Haan EA (2005). 2005 Annual Report of the South Australian Birth Defects Register, incorporating the 2005 Annual Report of Prenatal Diagnosis in South Australia. Adelaide. SA Birth Defects Register, Children, Youth and Women's Health Service, 2008.

Years 2006

Source: Gibson CS, van Essen PB, Scott H, Page C, Chan A, Haan EA (2009). 2006 Annual Report of the South Australian Birth Defects Register, incorporating the 2006 Annual Report of Prenatal Diagnosis in South Australia. Adelaide. SA Birth Defects Register, Children, Youth and Women's Health Service, 2009.

Years 2007

Source: Gibson CS, van Essen PB, Scott H, Baghurst P, Chan A, Scheil W (2007). 2007 Annual Report of the South Australian Birth Defects Register, incorporating the 2007 Annual Report of Prenatal Diagnosis in South Australia. Adelaide. SA Birth Defects Register, Children, Youth and Women's Health Service, 2010.

Years: 2008

Source: Gibson CS, Scott H, Baghurst P, Scheil W. (2012) Prenatal Screening for Congenital Anomalies in South Australia, 2008. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2012.

Years: 2009

Source: Gibson CS, Scott H, Baghurst P, Scheil W (2013). Prenatal Screening for Congenital Anomalies in South Australia, 2009. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2013.

Years: 2010

Source: Gibson CS, Scott H, Hayes AM, Scheil W (2014). Prenatal Screening for Congenital Anomalies in

South Australia, 2010. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2014.

Years: 2011

Source: Gibson CS, Scott H, Gower S, Scheil W (2011). Prenatal Screening for Congenital Anomalies in South Australia, 2011. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2014.

Years: 2013

Source: Gibson CS, Scott H, Scheil W (2017). Prenatal Screening for Congenital Anomalies in South Australia, 2013. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2017.

Years: 2014-2016

Source: Gibson CS, Scott H, Hernandez J. (2020). Birth Defects in South Australia 2016. Adelaide. SA Birth Defects Register, Women's and Children's Health Network, 2020.

Years: 2016-2017

Source: SA Perinatal Statistics Collection. Down's syndrome babies born in SA, 2016 and 2017. Prepared for Ellen Skladzien. 13 September 2021. SA Department of Wellbeing.

Victoria

Years 1976-2013

Source: Hui L, Muggli EE, Halliday JL (2015). Population-based trends in prenatal screening and diagnosis for aneuploidy: a retrospective analysis of 38 years of state-wide data BJOG. 2016 Jan;123(1):90-7. doi: 10.1111/1471-0528.13488. Epub 2015 Jun 25.

(data on the number of prenatal DS diagnoses)

Years: 1983-1998

Source: Riley M & Halliday J (2000). Birth Defects in Victoria 1983–1998, Perinatal Data Collection Unit, Victorian Government Department of Human Services, Melbourne, 2000.

Years 1995-2006

Source: Riley M & Halliday J (2008). Birth Defects in Victoria 2005–2006, Victorian Perinatal Data Collection Unit, Victorian Government Department of Human Services, Melbourne, 2008.

Years: 2007-2009

Source: Victorian Congenital Anomalies Register (2017). Congenital anomalies in Victoria 2007–2009. Melbourne: Consultative Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM), 2017

Years 2013-2014

Source: Victorian Congenital Anomalies Register (2017). Congenital anomalies in Victoria 2013–2014. Melbourne: Consultative Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM), Melbourne, 2017.

Years 2015-2016

Source: Victorian Congenital Anomalies Register (2018). Congenital anomalies in Victoria 2015–2016, Consultative Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM), Melbourne. 2018.

Years 2015-2016

Source: Hui et al. (2020). A minimum estimate of the prevalence of 22q11 deletion syndrome and other chromosome abnormalities in a combined prenatal and postnatal cohort. *Human Reproduction*, Vol.35, No.3, pp. 694–704, 2020. Advance Access Publication on March 24, 2020 doi:10.1093/humrep/dez286 (data on number of prenatal and postnatal diagnoses)

Years 2013-2019

Source: Pynaker C, Loughry L, Hui L, Halliday J. (2020). Annual report on Prenatal Diagnosis in Victoria 2019, The Victorian Prenatal Diagnosis Database, Murdoch Children's Research Institute 2020. doi: 10.25374/MCRI.14347436. (data on the number of prenatal DS diagnoses)

Western Australia

Years: 1966-1975

Source: Mulcahy MT (1979). Down's Syndrome in Western Australia: Cytogenetics and Incidence. *Hum. Genet.* 48, 67--72.

Years 1980-2014

Source: Report of the Western Australian Register of Developmental Anomalies, 1980-2014. <https://www.kemh.health.wa.gov.au/Our-services/Service-directory/WARDA/Reports>

Data for 1980-2004, also reported in:

Bittles AH, Bower C, Hussain R, Glasson EJ. 2007. The four ages of Down syndrome. *Eur J Public Health* 17:221–225.

New Zealand

Years: 1980-1992; 1994-2012

Source: Clearinghouse Annual Report 2014. International Clearinghouse For Birth Defects Surveillance and Research (ICBDSR)

Years: 1996-2020

Source: Personal email to the first author from Professor Barry Borman, Professor of Epidemiology, Director, Environmental Health Intelligence NZ, New Zealand Birth Defects Registry

S2. Modeling survival in DS

S2A. Constructing survival curves for DS

For modeling survival in DS, we followed the approach of de Graaf et al.⁴ Earlier, on the basis of multiple historical studies on the survival of persons with DS in developed countries, de Graaf et al. constructed DS-specific survival curves by year of birth.^{12,13} These curves were adapted for different ethnic groups in the U.S., based on the relationship between 1-year survival in these ethnic groups in general population and the 1-year survival in people with DS during the period 1983–2003, extrapolating this relation back in time, subsequently.¹³ The same approach was followed for adapting these curves for different U.S. states,¹² and for countries in Europe.⁴ The rationale for this adaptation is the assumption that a lower 1-year survival in the general population will be indicative for a less well-developed medical care system,

which will concomitantly impact the survival of children with DS. The procedure is described in detail in the Supplementary materials of de Graaf et al.,⁴ which can be downloaded at <https://www.nature.com/articles/s41431-020-00748-y>.

However, similar to de Graaf et al.,⁴ in this study, we only wanted to correct for situations in which a country had a clearly higher 1-year mortality in the general population than did the U.S. The U.S. model estimates were based on studies from diverse developed Western countries and, as such, were not specific for the U.S. only. In Australia and NZ, the general 1-year mortality was similar or lower than in the US. Therefore, we used the same survival curves as were used for the US in de Graaf et al. without adaptations.¹³

S2B. Comparison of constructed survival curves with Australian data on survival in DS

We have not found data on survival in DS for NZ. In Australia, however, this has been the focus of different studies.

Survival up to 10 years of age

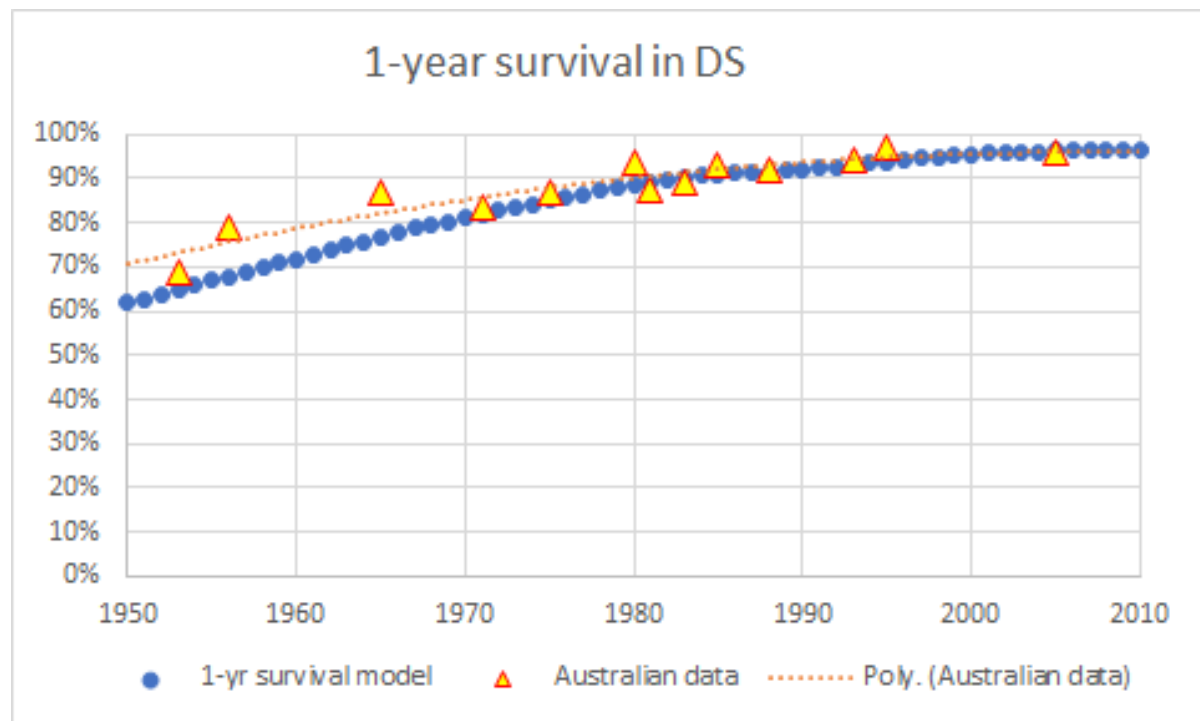
In the Table below, historical Australian research data on 1-, 5-, and 10-year survival rates are presented.

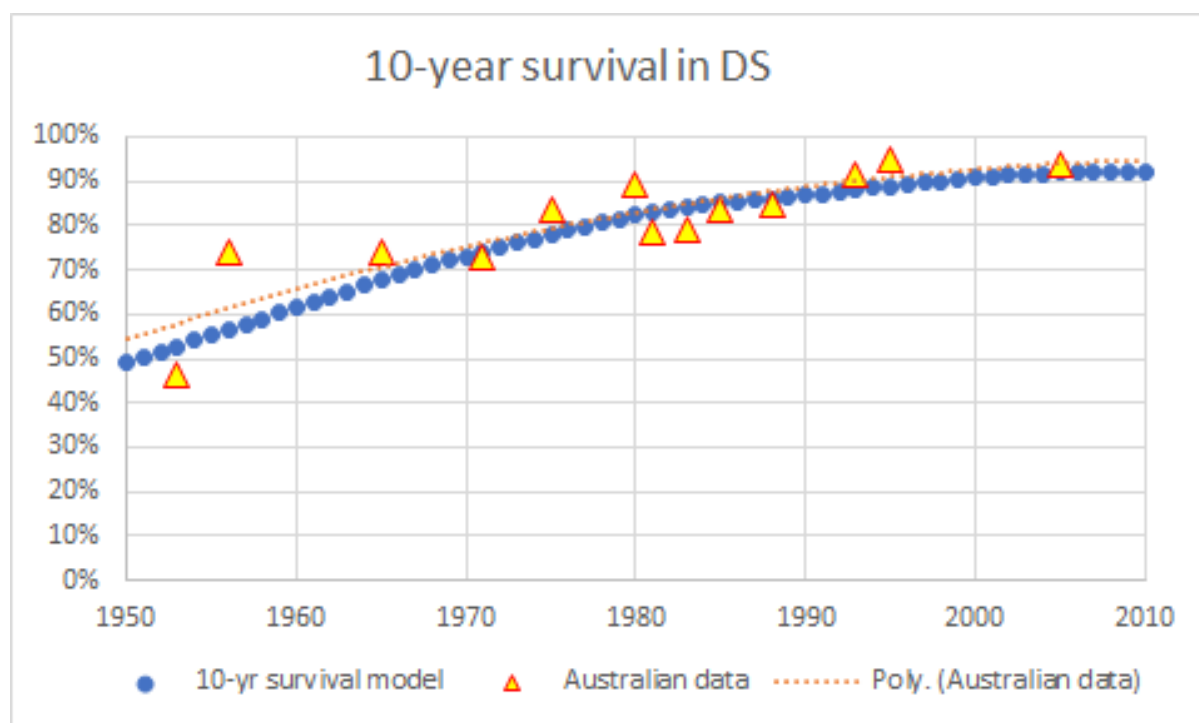
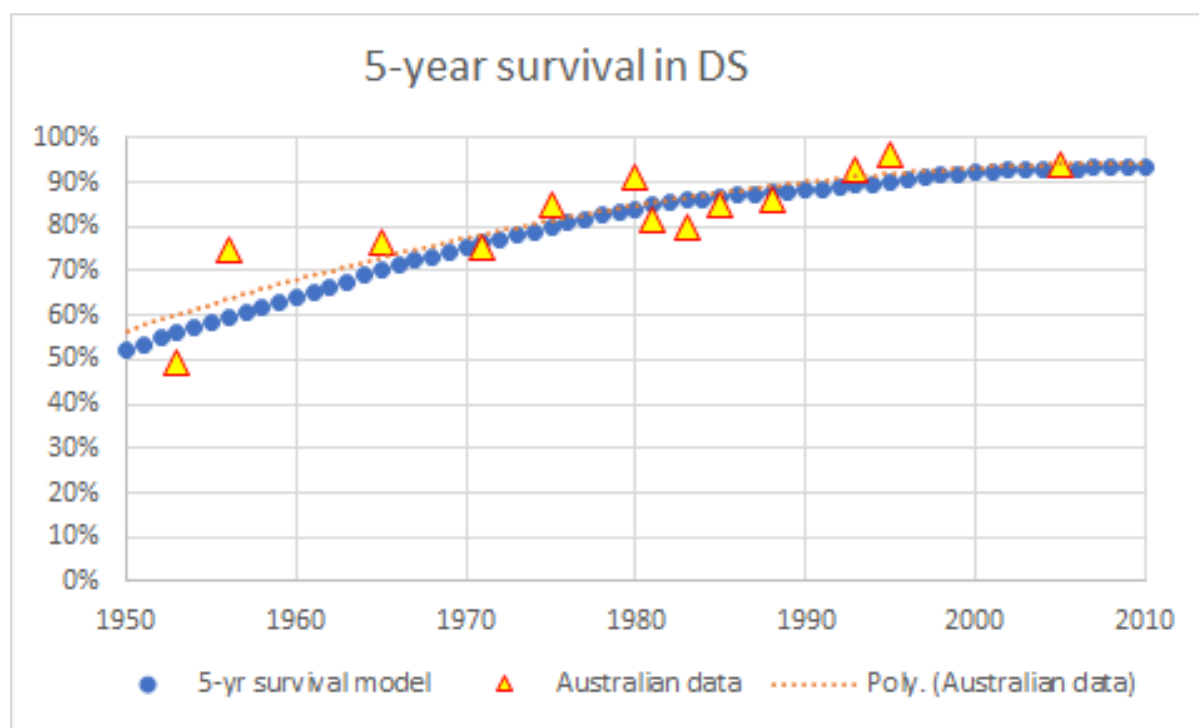
Table S1. 1-, 5-, and 10-year survival rates of children with Down syndrome in Australia

Study	Period	1-	5-	10-
		Year survival rates		
Collman & Stoller (1963) ¹⁴	1948-1957	68.9	49.4	46.2
Glasson et al. (2016) ¹⁵	1953-1959	79.2	75	74
Glasson et al. (2016) ¹⁵	1960-1969	86.9	76.6	74
Glasson et al. (2002) ¹⁶	1961-1970	94.0	86.7	84.0
Mulcahy in Maaskant (1993) ¹⁷	1966-1975	83.5	75.3	72.8
Glasson et al. (2016) ¹⁵	1970-1979	86.9	85.2	83.6
Glasson et al. (2002) ¹⁶	1971-1980	94.0	90.7	89.0
Malone (1988) ¹⁸	1976-1984	93.9	90.9	89.3
Bell, Pearn & Firman (1989) ¹⁹	1976-1985	87.4	81.4	78.4
Leonard et al. (2000) ²⁰	1980-1985	89.0	80.0	79.0
Glasson et al. (2016) ¹⁵	1980-1990	93	86	83.6
Glasson et al. (2002) ¹⁶	1981-1990	94.0	91.9	89.0

Leonard et al. (2000) ²⁰	1986-1990	92.0	86.0	85.0
Leonard et al. (2000) ²⁰	1991-1996	94.0	93.0	91.4
Glasson et al. (2016) ¹⁵	1990-1999	97	96	95.0
Glasson et al. (2002) ¹⁶	1991-2000	97.8	97.3	95.0
Glasson et al. (2016) ¹⁵	2001-2010	96	94	94

As one can see in Table S1, the 1-, 5-, and 10-year survival rates in the more recent study of Glasson et al.¹⁵ are consistently lower than the survival rates in Glasson et al.¹⁶ for corresponding periods of time. As the same surveillance database has been used, we would assume the more recent study to be based on the most up-to-date data. Therefore, in the graphs below, we have omitted the data from Glasson et al.,¹⁶ and used the data of Glasson et al.¹⁵ instead. In the graphs, a comparison is made between the models projections of these survival rates and the data from the Australian studies.





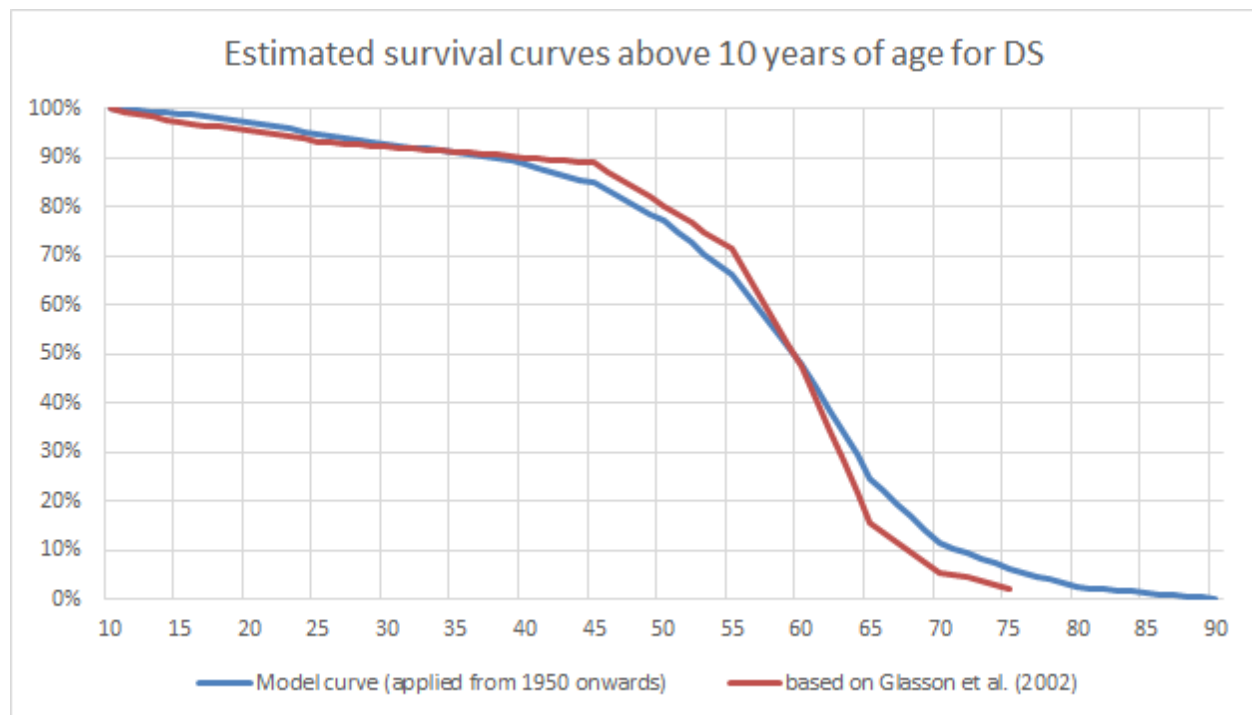
The (Western) Australian research data from the late 1950s and 1960s show higher values than projected by the model, though for 10-year survival only clearly for the late 1950s. This discrepancy might imply that survival improved more rapidly between the early 1950s and 1970 than we have modeled. However, it is also possible that the model is correct and that the study of Glasson et al.

overestimated the childhood survival for these older cohorts, as, in that day and age, some children will have died before they were diagnosed and registered by the Western Australian surveillance programs.¹⁵ If these early deaths are missed, 1-, 5-, and 10-year survival estimates will be too optimistic.

Survival beyond 10 years of age

For modeling survival rates beyond 10 years of age from 1950 onwards, de Graaf et al.^{4,13} made use of the average of (highly similar) survival curves for DS from 7 different historical studies, one from Australia—i.e., Glasson et al.¹⁶ For the period up to 1950, de Graaf et al.^{4,13} used a more hazardous curve based on Penrose.²¹

In the graph below, we compare our modeled survival curve beyond 10 years of age (as used from 1950 onwards) with the curve constructed by Glasson et al.¹⁶ The starting point is 100% alive at age 10.



The Figure above shows that differences between the curves are relatively small. Applying the curve based on Glasson et al.,¹⁶ instead of the model curve, would lead to an estimate of people with DS alive, as of 2020, which would be a few percent higher in the age range 40-60 (5%), and be substantially lower (33%) in the age range 65 years and older. However, as of 2020, in both estimates people above 65 years of age form less than 3% of the total population of people with DS. The estimate based on the Glasson curve (stretching it beyond 75 years of age by interpolating between the 75-year value of 2% to 0% at 90 years) would lead to a total for all ages of 5 year and older (as of 2020) that is less than a promille lower (0.07%) than the estimate on the basis of our model.

In Glasson et al.,¹⁵ a survival curve is presented up to 60 years of age for the cohort born between 1953–1959. If we take 10 years of age as the starting point, defining this as 100%, up to 55 years of age the curve is identical to the one presented in Glasson et al.¹⁶ However, between 55 and 60 years of age, the curve from Glasson et al.¹⁵ is less steep. We have compared our model curve with the 2002 curve, as that curve is constructed to 75 years of age.

For both Australia and NZ, we applied our constructed survival curves by year to the estimated numbers of LBs of children with DS by year to predict the number, by age group, of people with DS alive in the population. For further validation of the model (see Supplementary Materials S3), we also predicted the number of deaths of people with DS by age group for different years.

S2C. Sources for infant mortality in general population

For 1950–2015, data on infant mortality in the general population are available from the United Nations in File “MORT/1-1: Infant mortality rate (both sexes combined) by region, subregion and country, 1950–2100 (infant deaths per 1,000 live births)” in the World Population Prospects of the United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition.

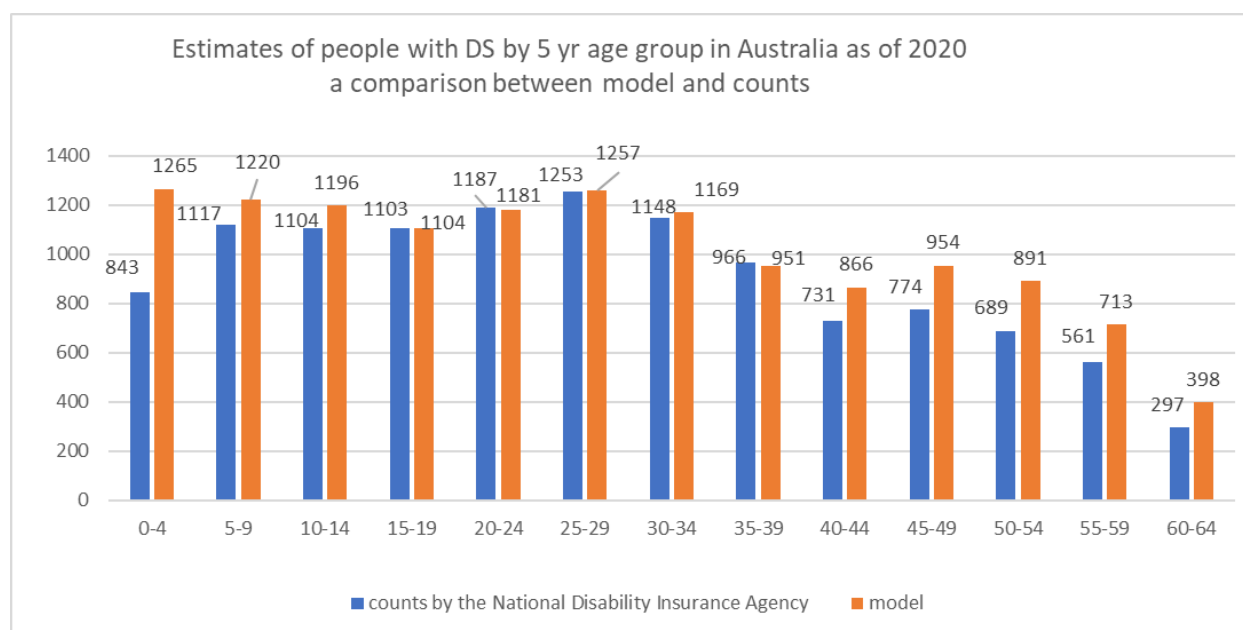
[https://population.un.org/wpp/DVD/Files/1_Indicators%20\(Standard\)/EXCEL_FILES/3_Mortality/WPP2017_MORT_F01_1_IMR_BOTH_SEXES.xlsx](https://population.un.org/wpp/DVD/Files/1_Indicators%20(Standard)/EXCEL_FILES/3_Mortality/WPP2017_MORT_F01_1_IMR_BOTH_SEXES.xlsx) (accessed November 9, 2018).

For the period 1900–1950, data on 1-year mortality rates in Australia and NZ could be found at <https://www.gapminder.org/data/> (accessed October 8, 2019)

S3. Validating the model

S3A. Comparison with population counts of people with DS

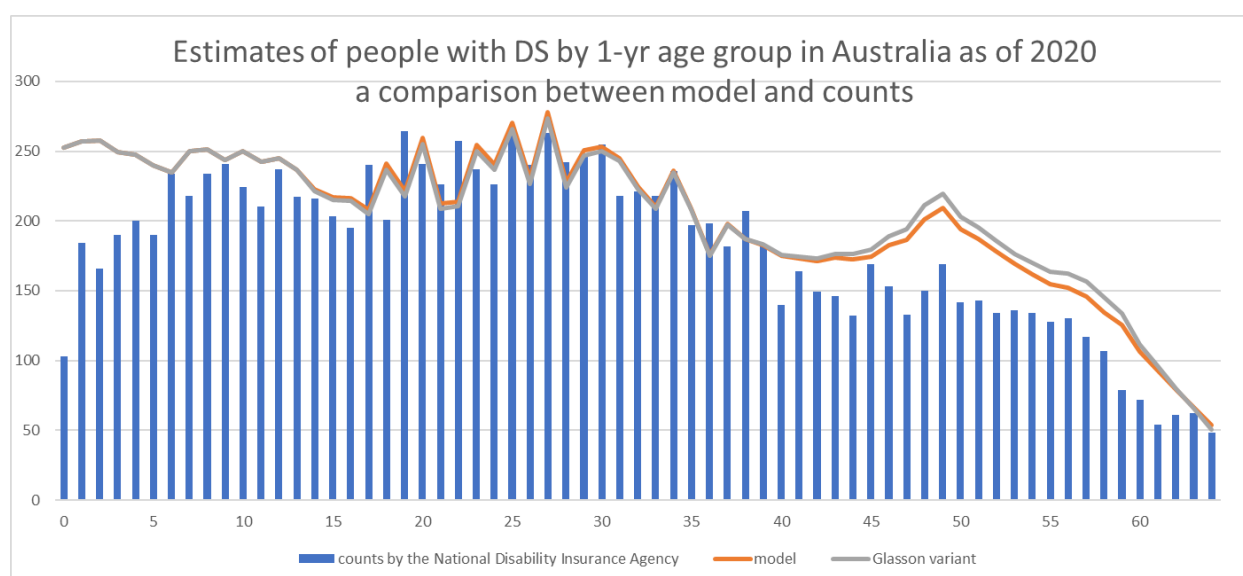
In Australia, the National Disability Insurance Agency (NDIA) is the primary access to support and services for people with permanent and significant disabilities. The NDIA collects data on the primary and secondary disability for all participants in the National Disability Insurance Scheme (NDIS). On request of Down Syndrome Australia, the NDIA has provided data on the number of participants with Down syndrome identified as a primary or secondary disability, by age group as of June 2020 (email on 19 January 2021). In the Figure below, we have compared our model predictions with these counts. In this graph, we have omitted people of 65 years of age and older, as one must be under 65 to enter the NDIS. Please note that this analysis is the sole responsibility of the authors of this study and has not been prepared in collaboration or partnership with the NDIA.



The model predicts 13,164 people with DS under 65 years of age as of 2020. The NDIA reports 11,773 (11% less).

There is a huge difference between counts and the model in the 0–4 year group. We assume this resulted from children who were eligible, but not yet enrolled in the NDIA. Between 5 to 40 years of age (so people born in the period 1980–2015), the model and the counts are highly similar. Above 40 years of age, the model predicts more people than counted by the NDIA, as of 2020.

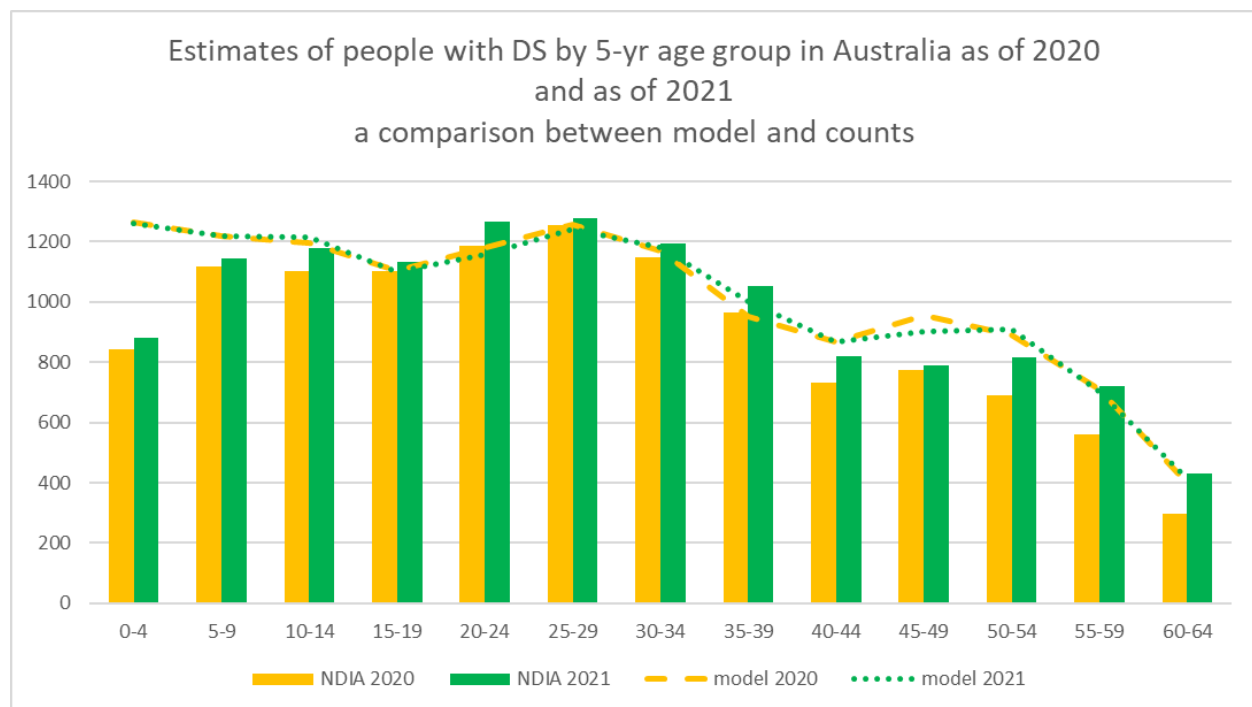
As the Figure below shows, the alternative survival model, based on the survival curve above 10 years of age derived from Glasson et al.,¹⁶ does not lead to a better match with the NDIA data.



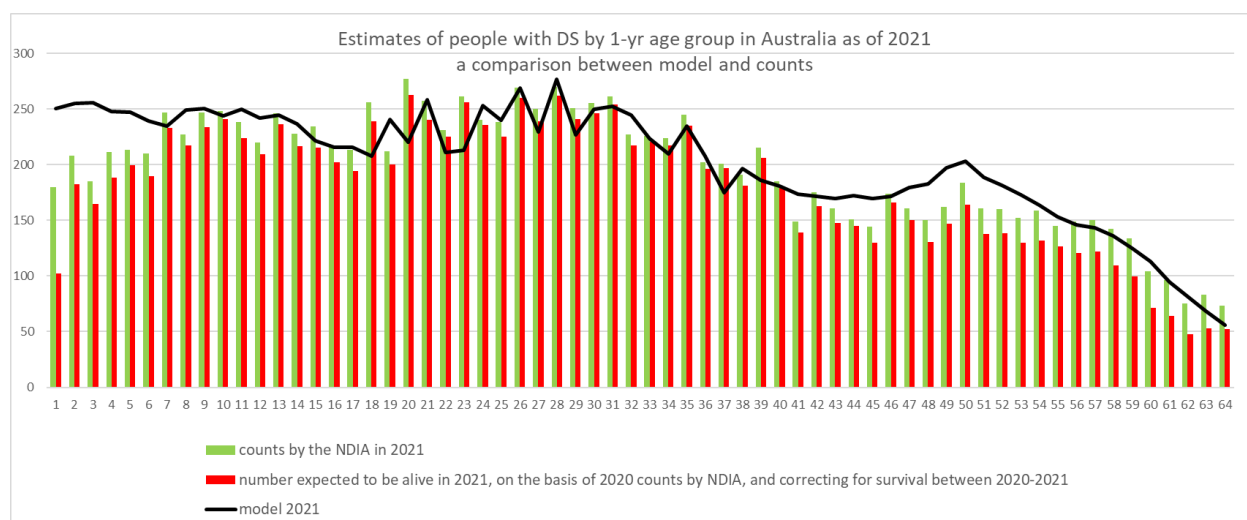
Our best hypothesis regarding people with DS aged 40 and older is that they, and their families, have been managing without government support for a long time, and they are probably not accustomed to seeking support for employment or therapies, and therefore may have a slower uptake on average to the NDIS. The NDIS was progressively introduced in Australia from 2013 and reached full roll out in 2020.

In the 0-5 year age group, the NDIA number is much lower than our models estimate. However, this is likely the result of delays in parents of young children applying for access to the NDIS, and the NDIA needing some time to process these applications.

To check if there indeed are delays in uptake, we requested the NDIS data for 2021 (as of June 2021) on DS. In the graph below, we compare our model predictions for 2020 and 2021 with the 2020 and 2021 counts in the NDIA. The match between model and counts is clearly better for 2021. The model predicts 13,338 people with DS under 65 years of age as of 2021; the NDIA reports 12,708, a difference of only 3%. If we exclude the 0-4 year olds, the difference is 0.7%.



In all age groups, the NDIS data includes more people with DS in 2021 as compared to 2020. On the basis of the counts in the NDIS data from 2020, applying our survival model to these data, we estimated how many of these people would still be alive a year later. In the graph below, these estimates, the actual NDIS counts in 2021, and our model projections for 2021 are presented. The 0-year olds (age in 2021) are excluded, as these were not yet born in 2020.



The graph shows new enrollments in almost every 1-year age group. The increase is the strongest in the very young children, confirming our assumption that there are clear delays in parents of young children with DS applying for access to the NDIS. The fact that there is still a discrepancy between the model and counts in this age group, as of 2021, is very likely the result of young children not yet being enrolled.

If we assume that the increase between 2021–2020 is the result of a structural delay in enrollment of young children, one could extrapolate the annual increase by age to the situation in which the 0–6 year olds in 2021 are 7 years of age (see Table below). To estimate the number of enrolled 7 year olds in 2022, we take the number of 6 year olds enrolled in 2021 and add 6% (which was the increase for this age group from 2020 to 2021). The number of 7 year olds enrolled in 2023 will be the number of 5 year olds enrolled in 2021 plus 11% (the increase for this age group between 2020 and 2021), and that total plus 6%, etc. This would imply that the 1,552 children who were 0–7 years old and enrolled in 2021 would have increased to 2,165 enrolled at age 7 (in the corresponding year). Our demographic model projects 1,982 children alive in 2021 in the age range of 0–7 years. Applying model survival rates, this number translates to 1,946 alive at age 7, a bit lower even than the above estimation of 2,165 enrolled children. This calculation shows that slow enrollment of young children could probably explain the discrepancy between the NDIS and our model for those under 7 years of age.

age in 2021	Number of persons with DS per NDIA in 2021	Number of persons with DS per NDIA in 2020	increase 2020–2021	Number of persons with DS expected to be in the NDIA at age 7, applying these annual increase percentages	Number of persons with DS alive in 2021 according to our model	Number of persons with DS alive at age 7, according to our model
0	98			298	253	243

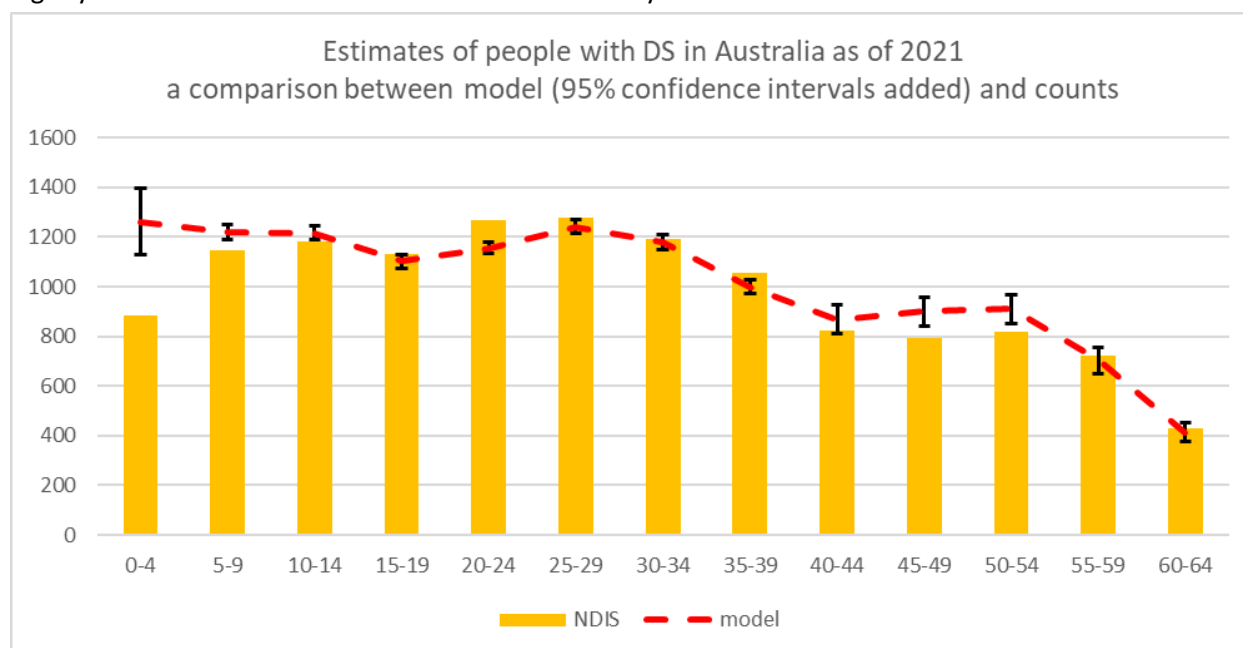
1	180	103	75%	313	251	242
2	208	184	13%	320	255	248
3	185	166	11%	255	256	251
4	211	190	11%	262	248	245
5	213	200	7%	249	247	245
6	210	190	11%	222	239	238
7	247	234	6%	247	234	232
total	1,552			2,165	1,982	1,946

An increase in enrollment is also clearly visible in the 50–64 year olds. As a result, especially for the age 54–64, the match between counts and model, as of 2021, is much better than it is for the data from 2020. However, for people in their forties and early fifties, as of 2021, the model and counts still differ. There is also an increase in enrollment from 2020 to 2021 for this age group, but we assume that not yet all people in this age range are enrolled in the NDIS, as of 2021. The alternative explanation might be that the model overestimates for the matching years of birth (1957–1971), with either too high estimates of actual birth prevalence or an underestimation of mortality in this period. However, this first explanation seems unlikely, as the numbers of DS-related terminations were low in this period. There is no indication in the literature (see S1C) that this is otherwise, so birth rates in this period are mainly determined by maternal ages. We have used reliable sources on maternal age (see S1A). The second explanation seems unlikely, too, as the alternative model for survival, based on Australian specific data, predicts even more people alive from these years of birth.

In the 20–39 years range, as of 2021, the NDIS appears to count more people (5%) than we modeled. It is possible that either the surveillance programs for the corresponding years of birth (1982–2001) had some underascertainment and/or survival was more favorable than modeled for these years.

We examined the possibility that some of the discrepancies between the 2021 model and the 2021 counts are the result of chance. In our modeling, if data for certain states were unavailable the numbers for that state were estimated on the basis of the actual LB prevalence in states with known numbers. Even if there are no systematic differences between states, this procedure introduces a prediction interval, which can be estimated. The same applied to the estimation of DS LBs, absent DS-related

terminations. Subsequently, our modeling applied survival chances to the estimated number of LBs in each year of birth, up to the year under observation, to estimate the number of people with DS still alive. Even if these chances are perfectly correct, the procedure introduces a prediction interval. The combined effect of these intervals (for 5-year groups) were estimated using a Monte Carlo simulation with 10,000 iterations. With the exception of the youngest group, the confidence intervals are small. Out of the age groups in the 20–39 age range, the counts are within the model’s confidence interval for the age group 30–34 years, and almost for 25–29 years. However, for 20–24 years (representing a year of birth between 1997–2001) and for 35–39 years of age (representing a year of birth between 1982–1986), we think the most plausible explanation is that the birth defects surveillance programs have slightly under-counted the number of DS LBs in those years.



S3B. Comparison of age at death of people with DS

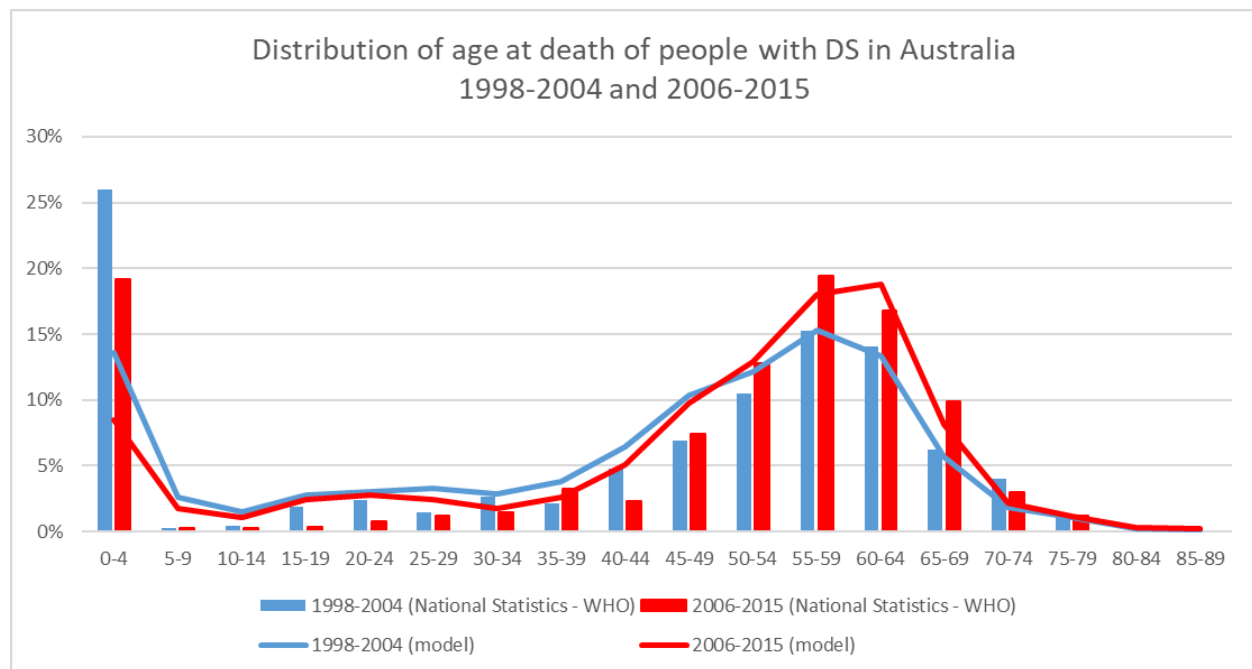
The WHO Mortality DataBase (MDB) comprises deaths registered in national vital registration systems, with underlying cause of death coded by national authorities. The raw data can be downloaded at https://www.who.int/healthinfo/statistics/mortality_rawdata/en/ (accessed September 17, 2019).

As national systems can be incomplete, and as deceased people with DS will not always be registered as having died with DS as the primary cause of death, these data cannot be interpreted as covering every deceased person with DS in a country. Assuming “under-registration” is not dependent on the age of the person, one could consider these data as a depiction of the age distribution of deaths of people with DS, which can be compared to the distribution of the age at death as predicted by our model.

Australia

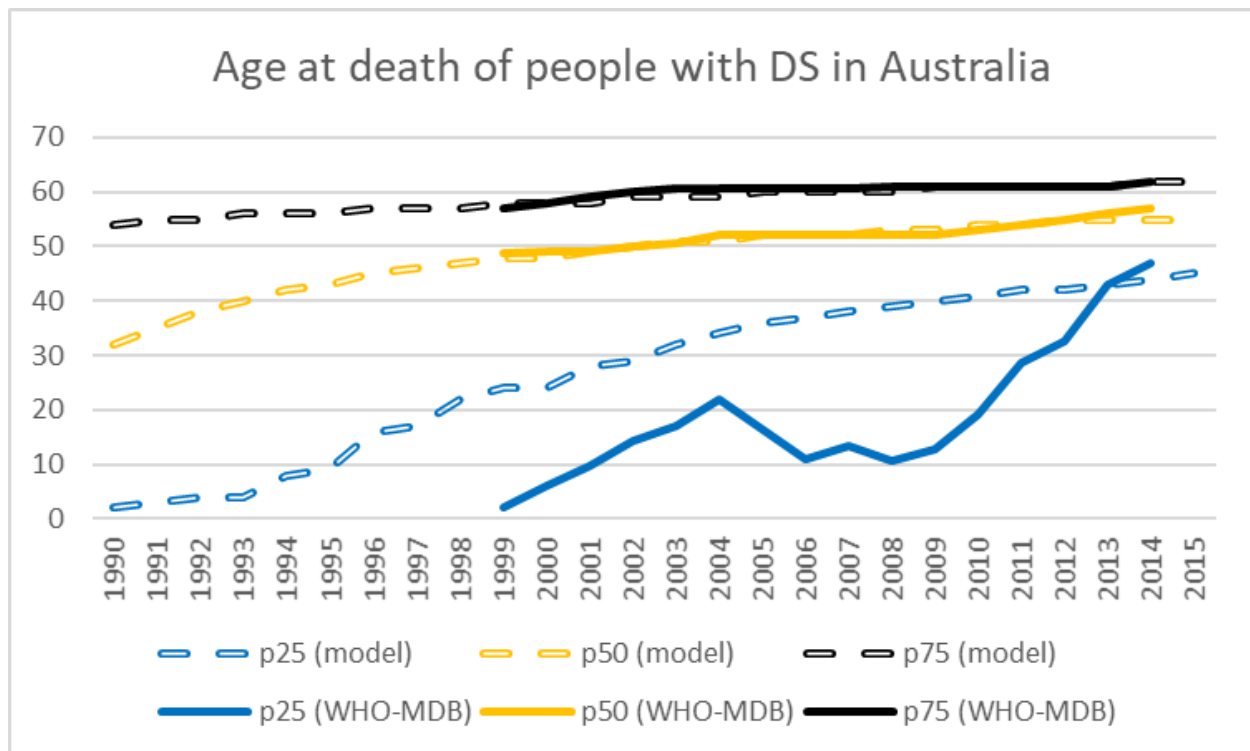
For Australia, the WHO Mortality Database has data available for 1998–2015 (with 2005 missing). The MDB contains data on 767 people with DS who died between 2006–2015, which is 38% of the number

projected by the model for the same period. For 1998–2004, it is 420, and 40%, respectively. For 2006–2015, correlation between MDB and model is 0.91 ($p < 0.000$); for 1998–2004, it is 0.89 ($p < 0.000$). The Figure below shows the results of the comparison.



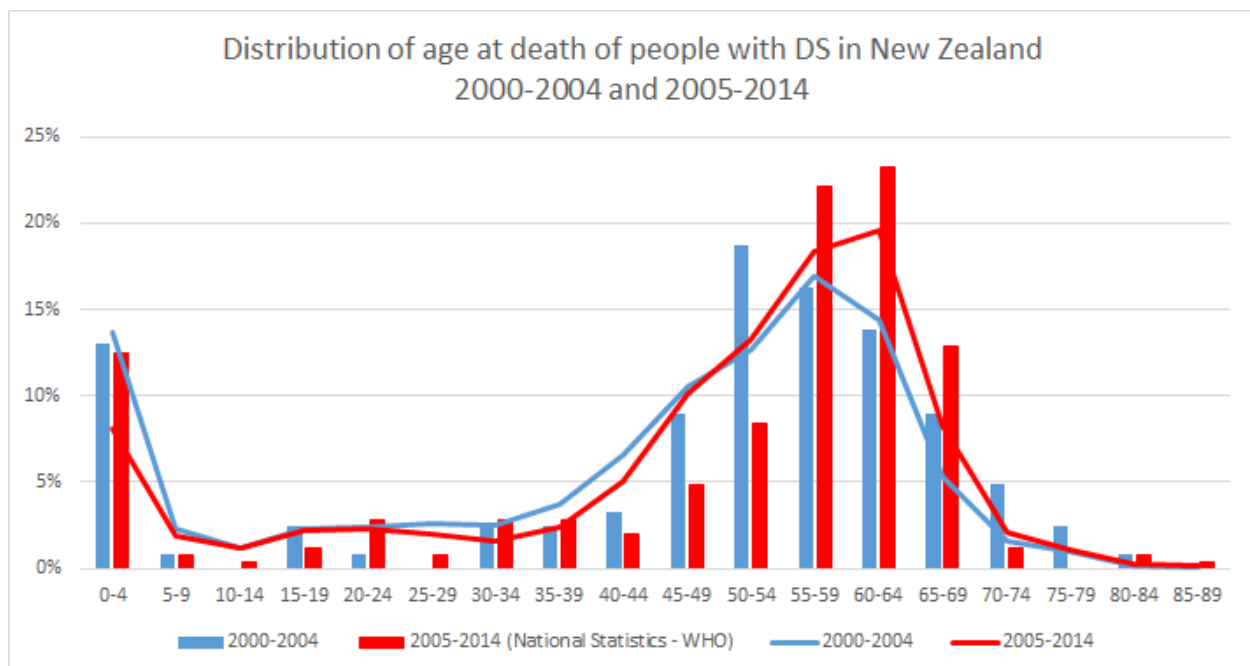
The percentage in the age range 0-4 years in our model is much lower than in the counts. De Graaf et al. found the same for many European countries.⁴ Probably, the assumption that “under-registration” is independent of age, is not correct for infants with DS. If a child with DS died in the first year of life, the chance to be reported with DS as primary cause of death is probably higher than later in life, because a doctor would be more inclined to allocate DS as primary cause of death in this age group. Leaving out the 0–4 years of age group from the analysis, leads to a higher correlation between MDB and model of 0.98 ($p < 0.000$) for 2006-2015; and of 0.96 for 1998-2004 ($p < 0.000$).

In addition, we have estimated the 25th percentile, 50th percentile, and 75th percentile of these ages of death by year. In analyzing the WHO data, we used 5-year running averages. For the first and last data point in each time series, we used 3-year averages. The Figure below shows the results of the comparison. The discrepancy for the 25th percentile probably is a result of the “relative overrepresentation” of DS as primary cause of death in the very young children in the Australian MDB data.

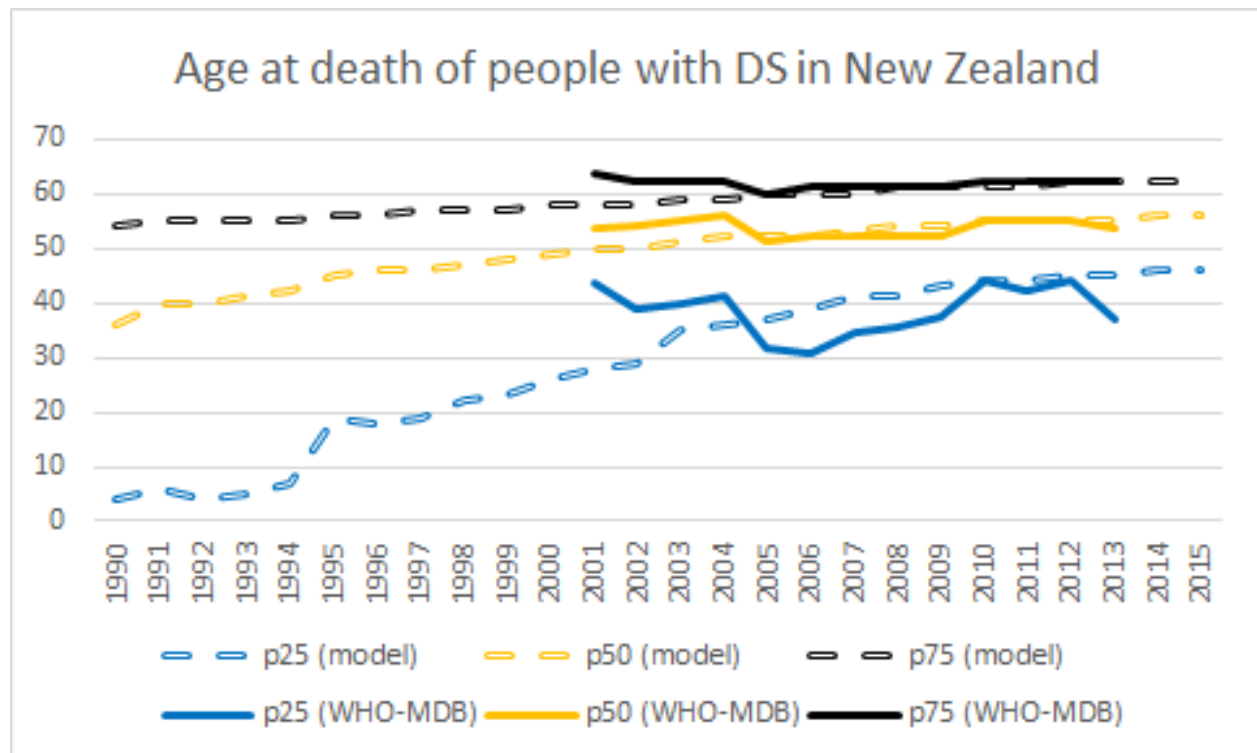


New Zealand

We followed the same procedures for New Zealand. For NZ, the WHO Mortality Database has data available for 2000–2015. The MDB contains data on 249 people with DS who died between 2005–2015, which is 50% of the number projected by the model for the same period. For 2000–2004, it was 123 and 61%, respectively. For 2005–2015, correlation between MDB and model is 0.93 ($p < 0.000$); for 2000–2004, it is 0.93 ($p < 0.000$), too. The Figure below shows the results of the comparison.

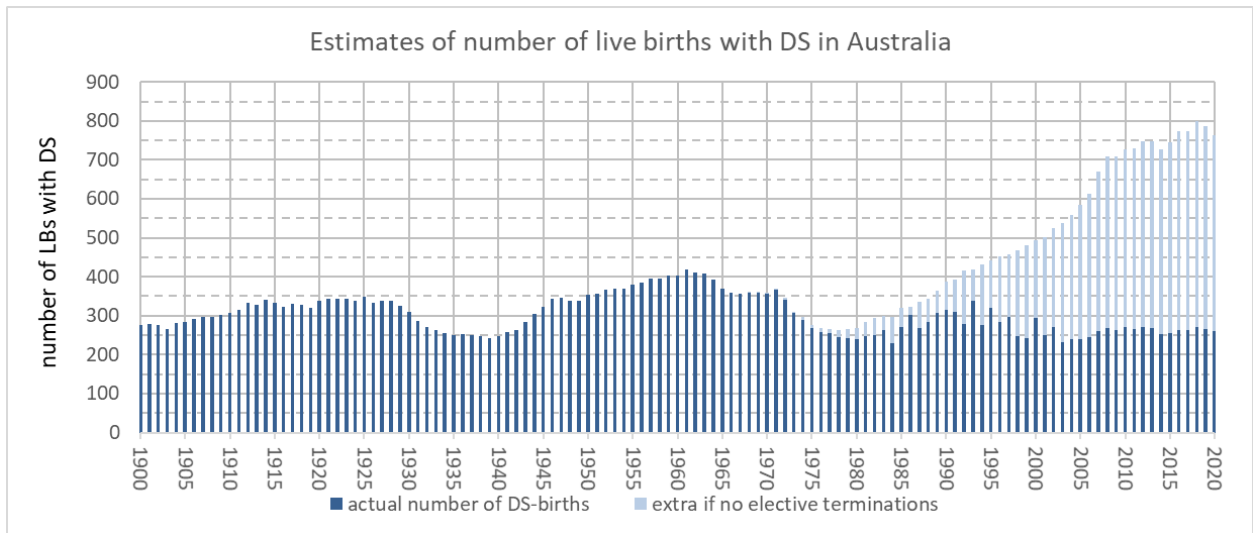


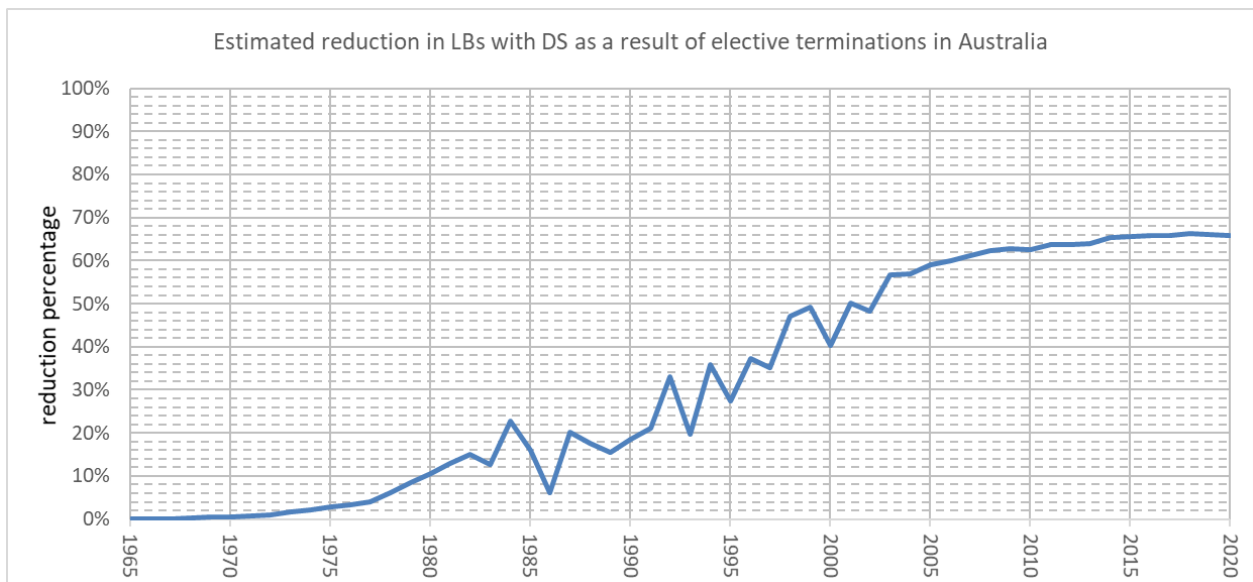
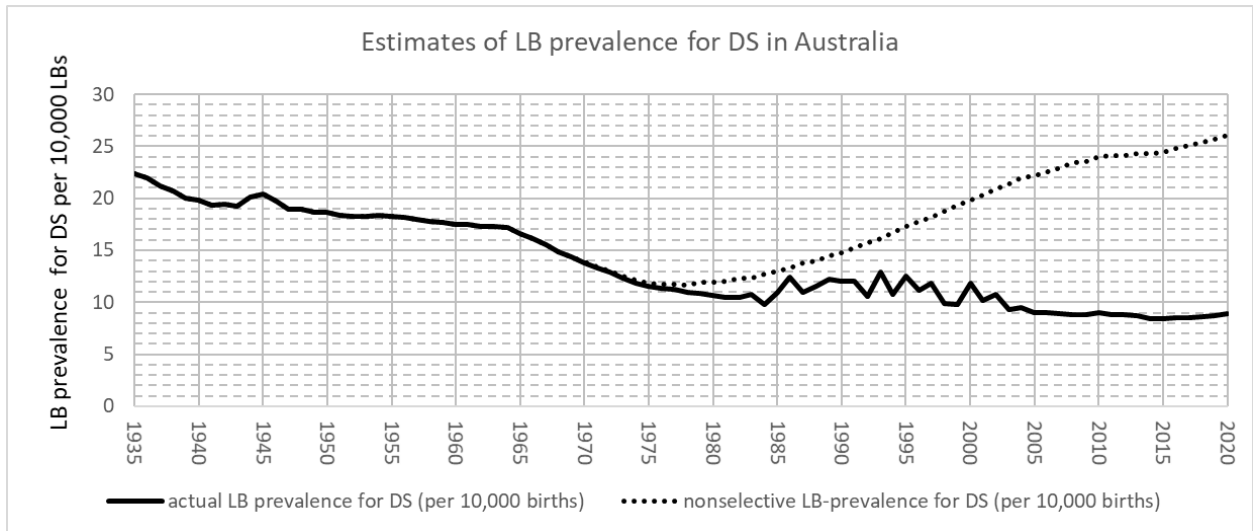
The analysis in terms of the 25th percentile, 50th percentile, and 75th percentile of age of death by year, is depicted in the Figure below, and shows a fairly good fit.

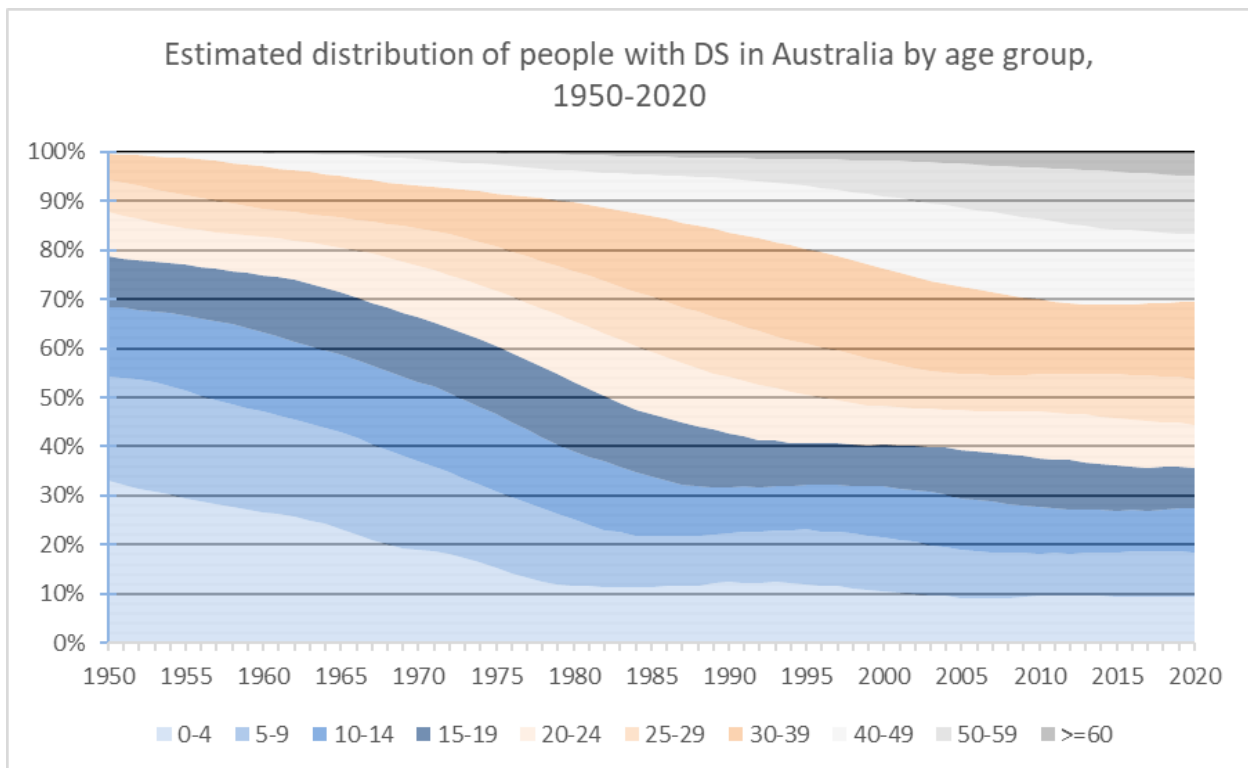
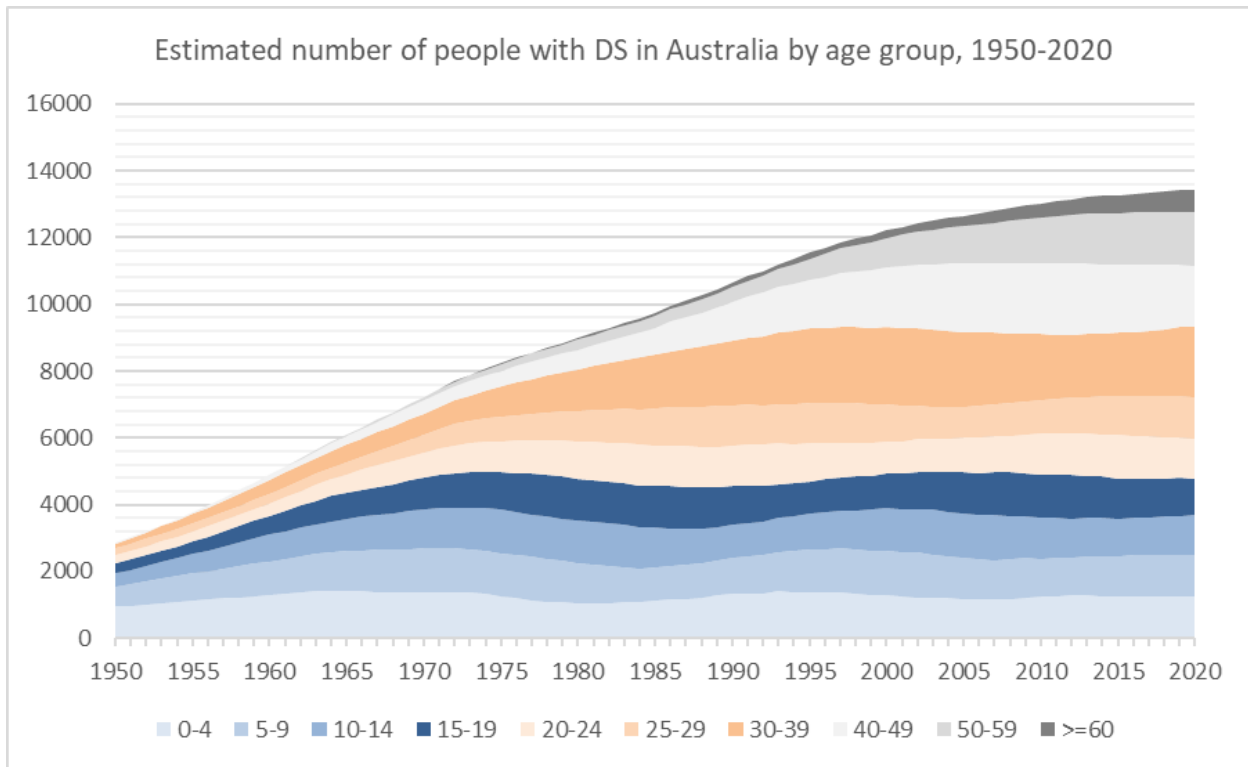


S4. Results

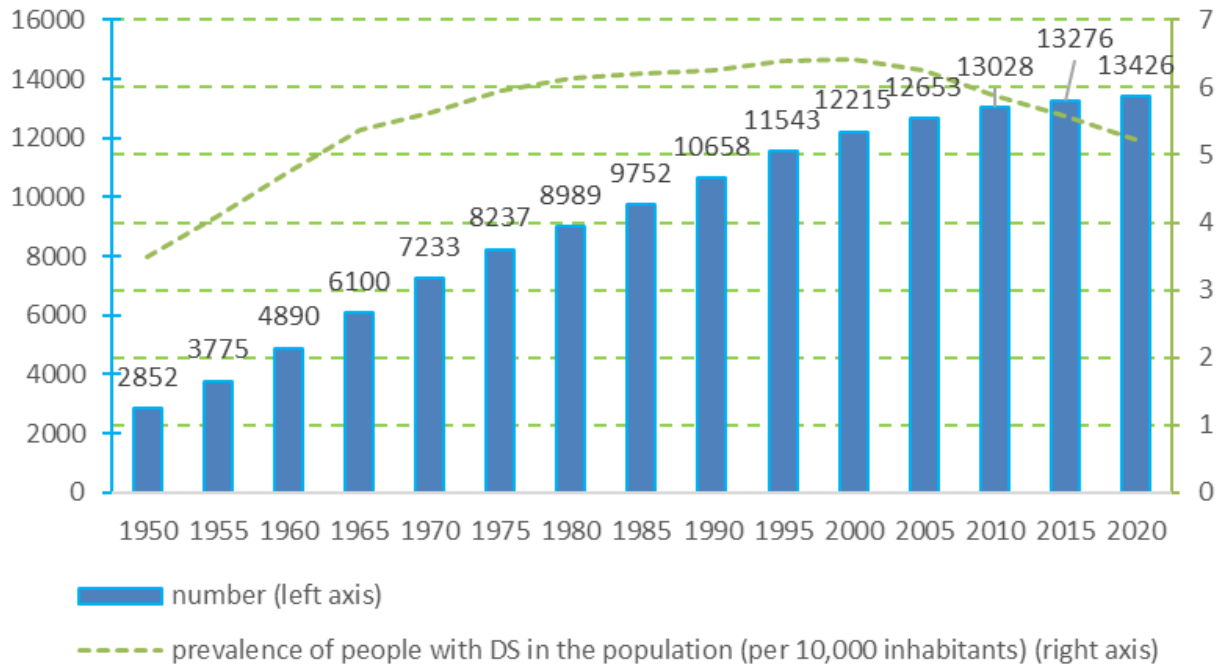
Australia



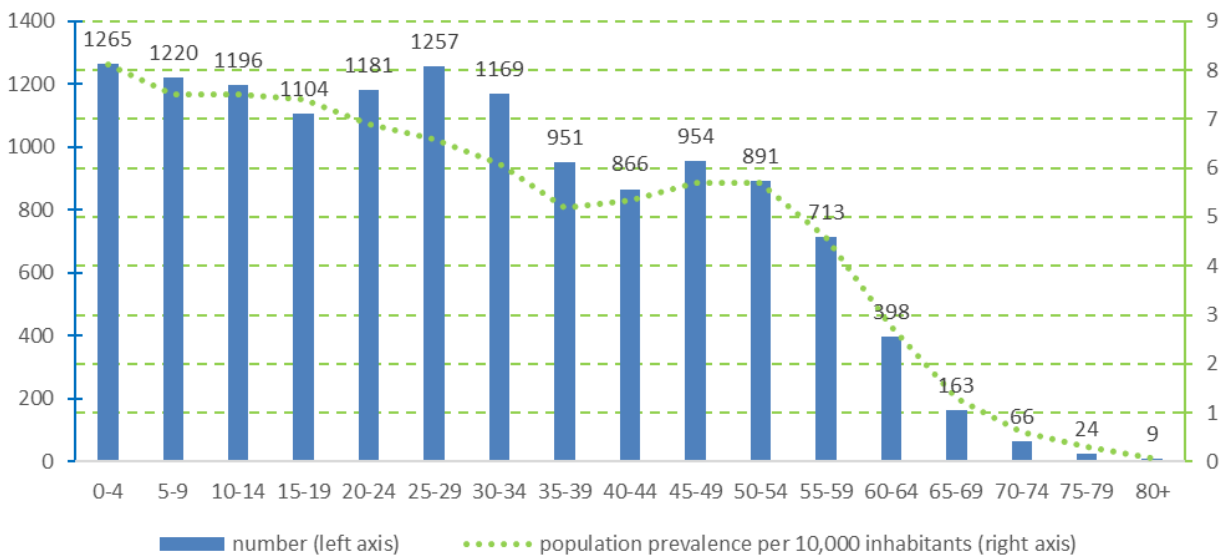




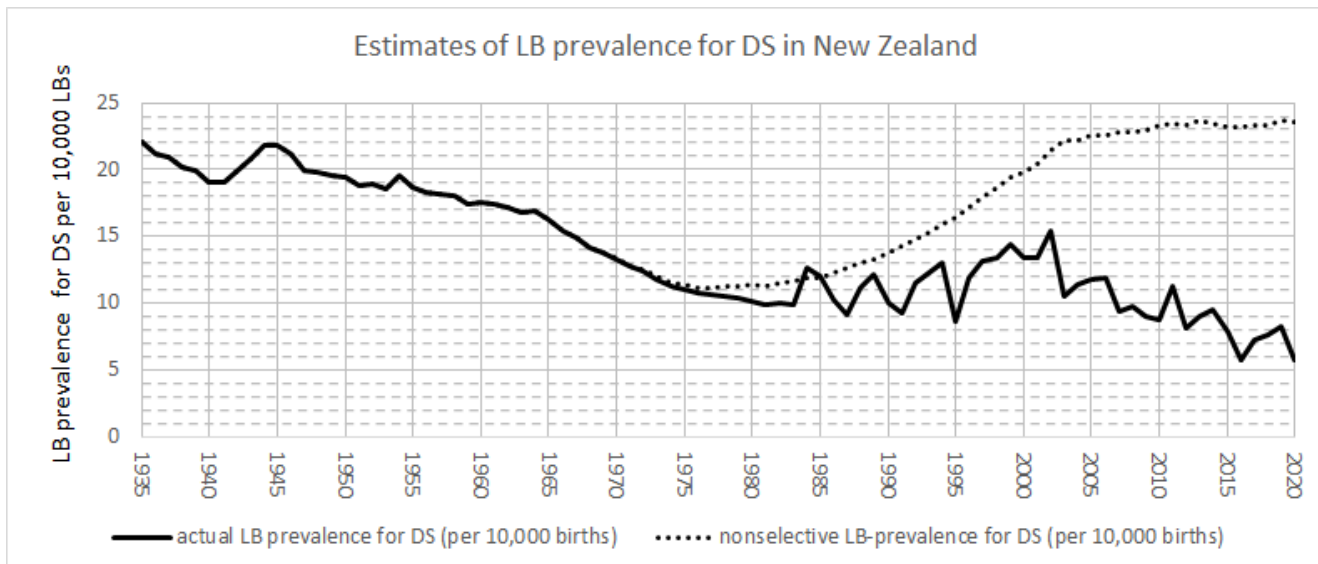
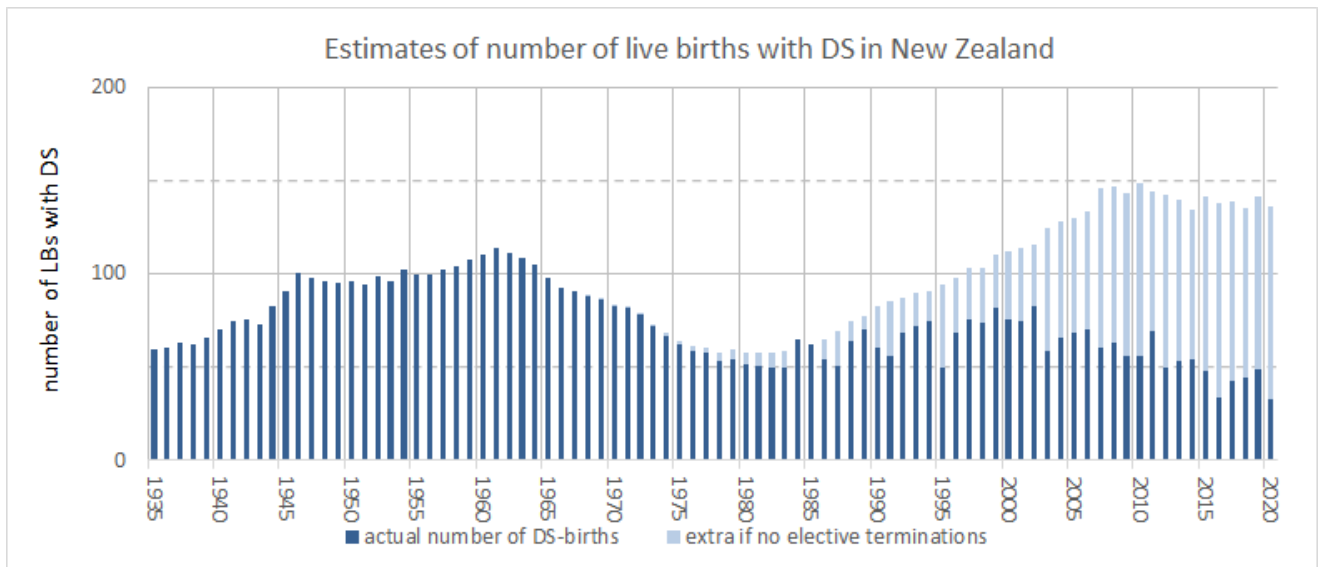
Estimated people with DS in Australia, 1950-2020

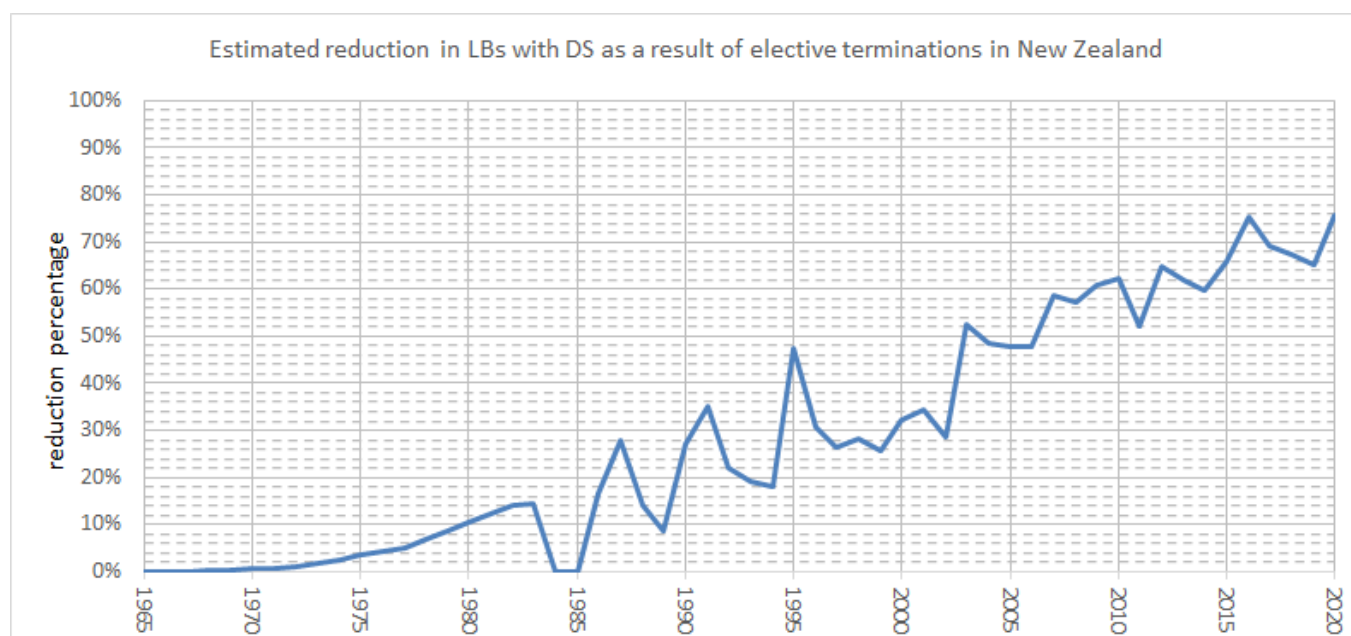


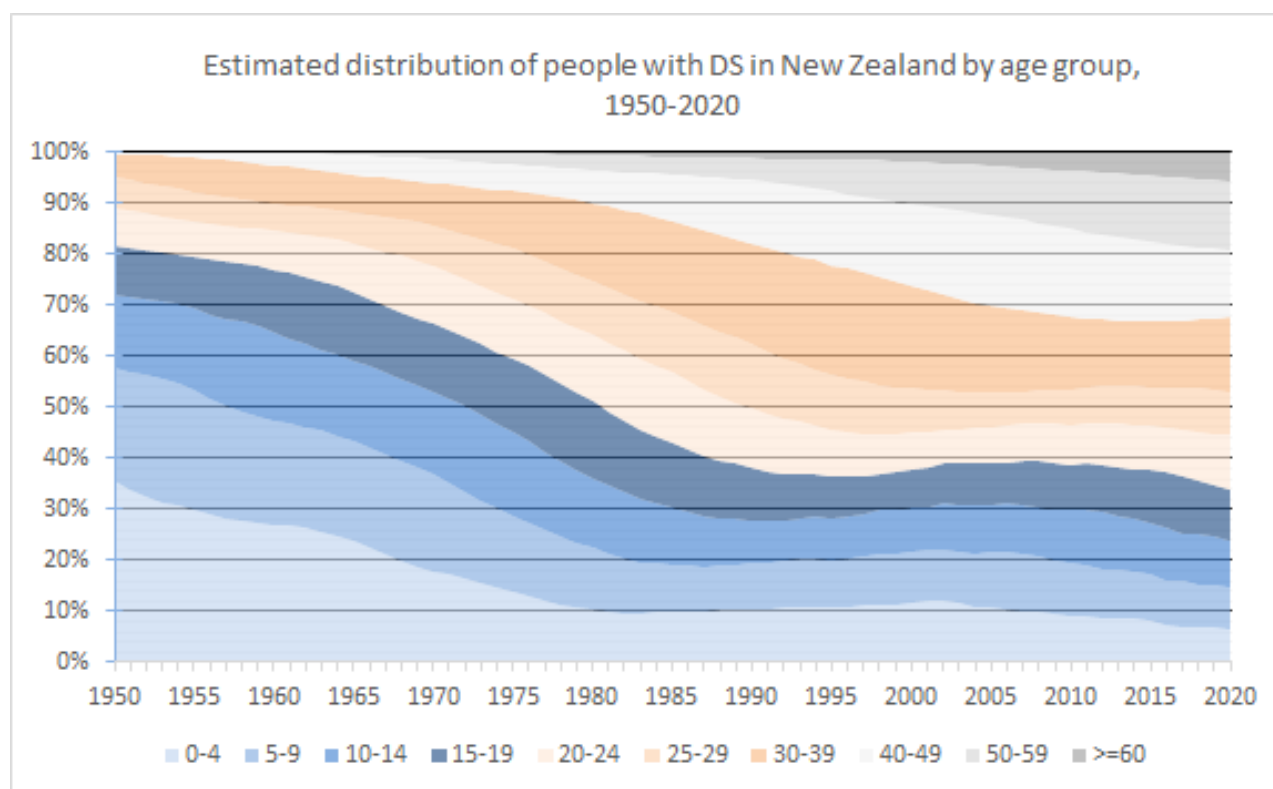
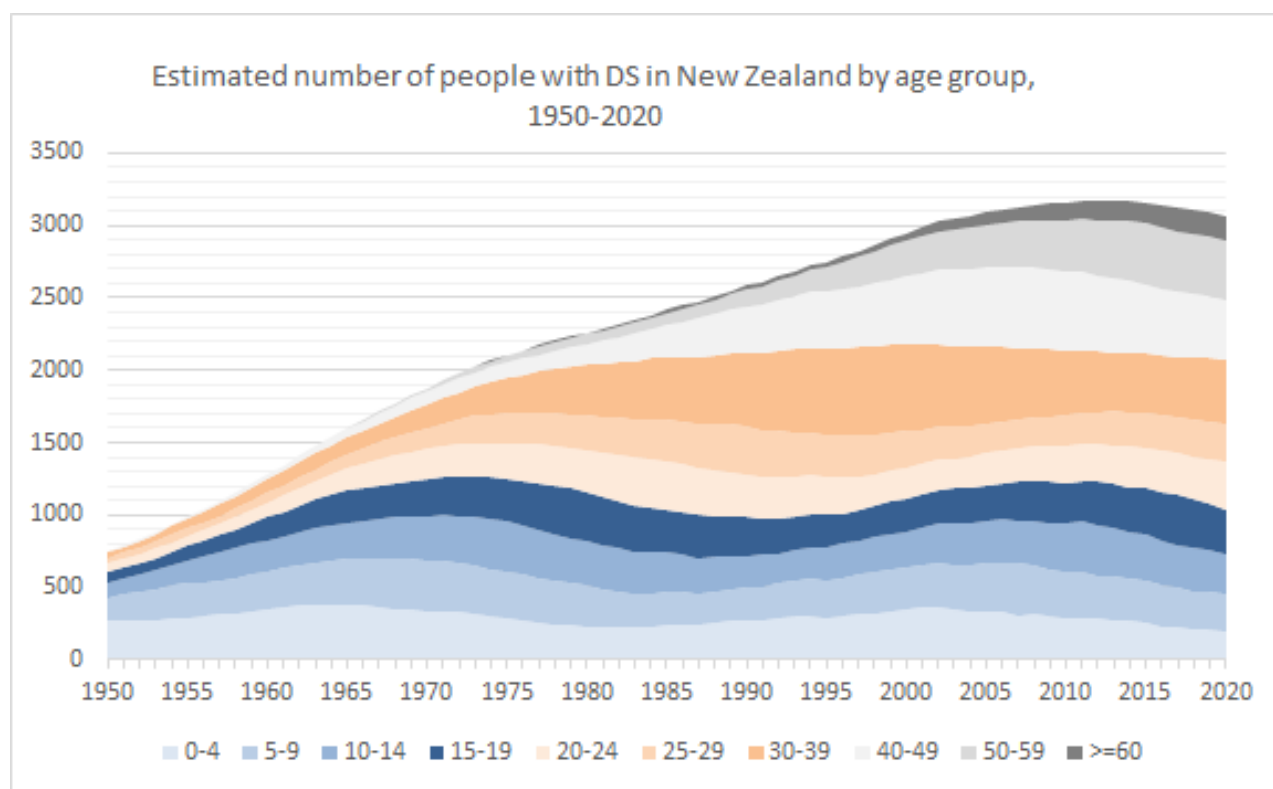
Estimated people with DS in Australia by age group, as of 2020

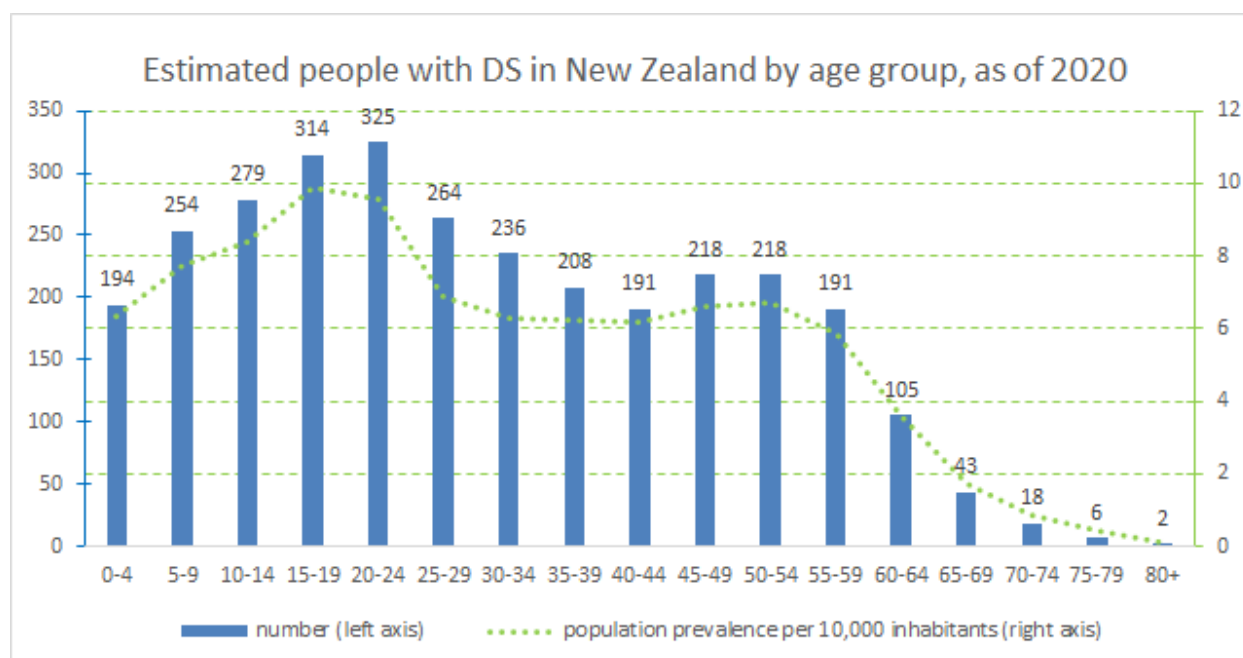
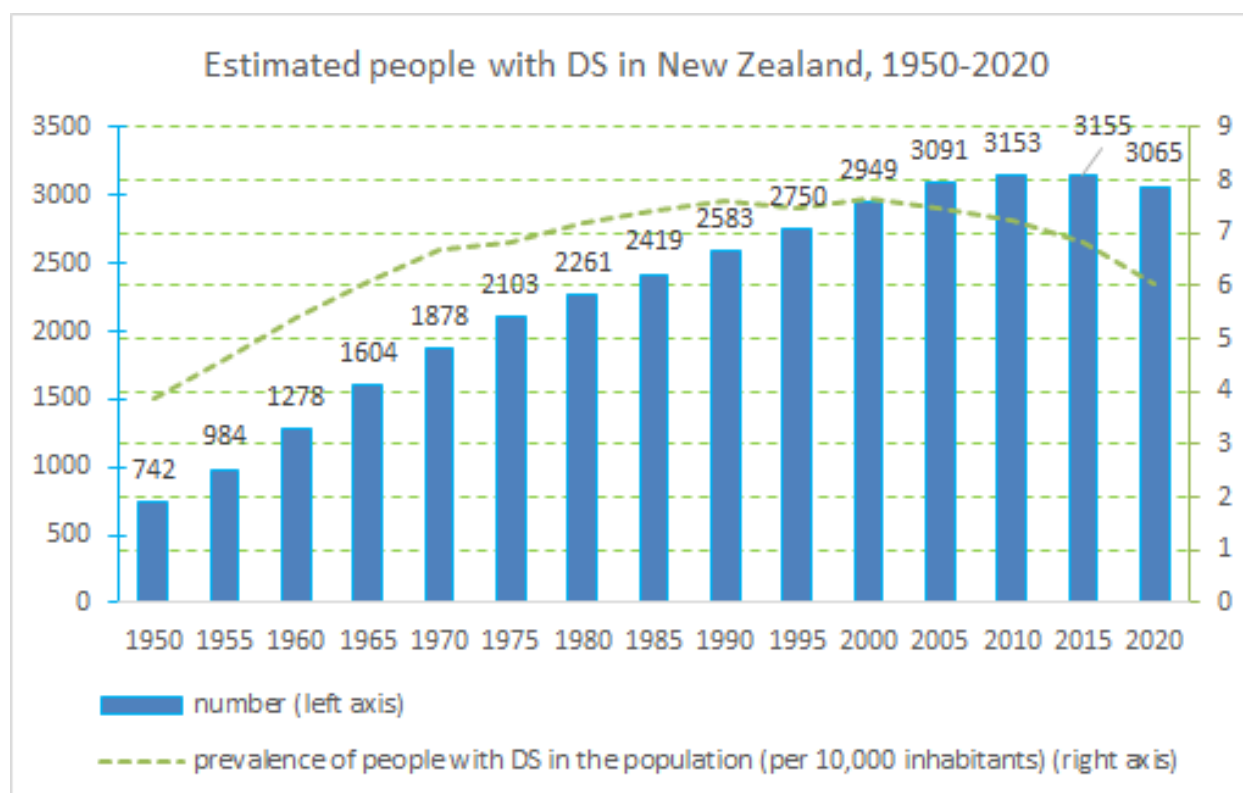


New Zealand









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