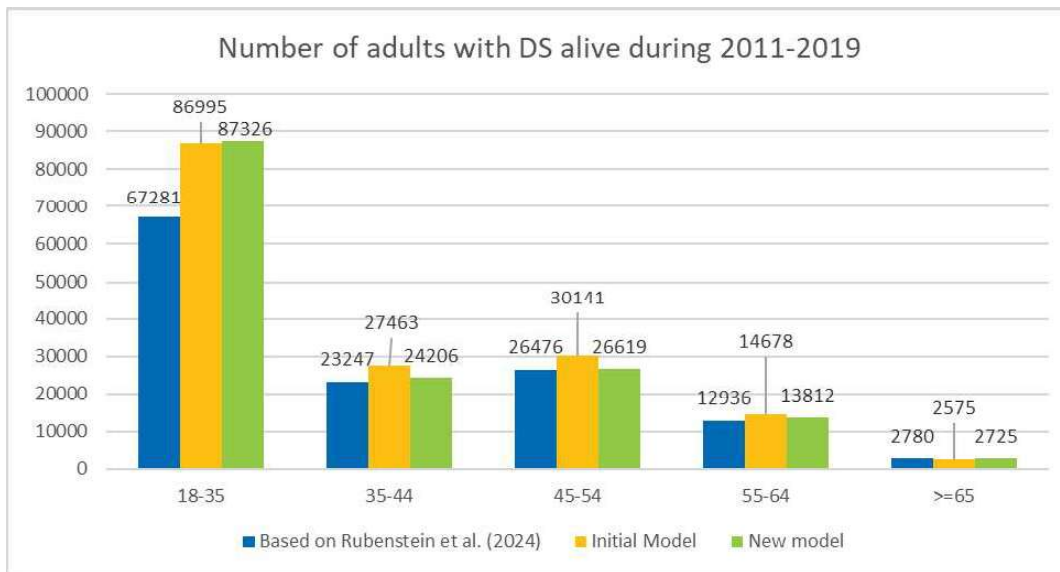


**United States (U.S.)**

In the U.S., Rubenstein et al. (2024) studied data from Medicare and Medicaid.<sup>39</sup> Their research was primarily focused on mortality and Alzheimer disease in DS. However, their data can be used for comparison with our model. They counted the number of adults with DS enrolled in Medicare and/or Medicaid in the period 2011–2019 and published the numbers by age at first enrollment. If we assume that everyone with DS is enrolled immediately at 18 years of age, the numbers and age distribution could be predicted by the modeled numbers of people with DS alive in 2011, and, added to the group 18–35 years of age, the people with DS that turned 18 years of age during 2012–2019. In the figure below, the results of the initial model and the new model are compared with the data from Rubenstein et al.<sup>39</sup>



Both models predict much higher numbers in the youngest group. Probably part of young adults (around 22%) with DS are not yet enrolled in Medicare and/or Medicaid. For the age groups above 35 years of age, the results of the new model are very close to the data of Rubenstein et al.<sup>39</sup>

### **S3B. Comparison of age at death of people with DS**

Another way of validating the model is comparing age at death data of people with DS from national statistics with model predictions of the age distribution of deaths of people with DS.

The WHO Mortality DataBase (MDB) comprises registered deaths by country (or territory), 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/](https://www.who.int/healthinfo/statistics/mortality_rawdata/en/) (accessed September 17, 2019).

The current link for these files is

<https://www.who.int/data/data-collection-tools/who-mortality-database>. Deceased people with DS will not always be registered as having died with DS as the primary cause of death. Assuming “under-registration” is not dependent on the age of the person, one could look at the age distribution of deaths of people with DS and compare this with the model predictions.

Below, we have made this comparison. If the database had annually fewer than, on average, 15 deaths of people with DS, we considered this a too small base for comparison with the model. We have included the 4 comparison countries (UK, France, Australia, and the U.S.) to check if the new model works well for these countries in this regard.

#### **Countries/territories in the Caribbean**

##### *Anguilla*

No data on age at death available.

##### *Antigua and Barbuda*

No data on age at death available.

##### *Aruba*

Data for only 2008, 2011, and 2013–2015. And on average 1 death (of someone with DS as primary cause of death) per year reported. Not enough data to make a comparison.

##### *Bahamas*

Data for only 2002–2004, 2006–2007, and 2011–2014. And on average 3 deaths per year are reported. Not enough data to make a comparison.

##### *Barbados*

Data for only 2002–2003, 2005–2006, 2008–2009, 2011, and 2013. And on average 1 death per year reported. Not enough data to make a comparison.

##### *Bonaire*

No data on age at death available.

##### *British Virgin Islands*

No data on age at death available.

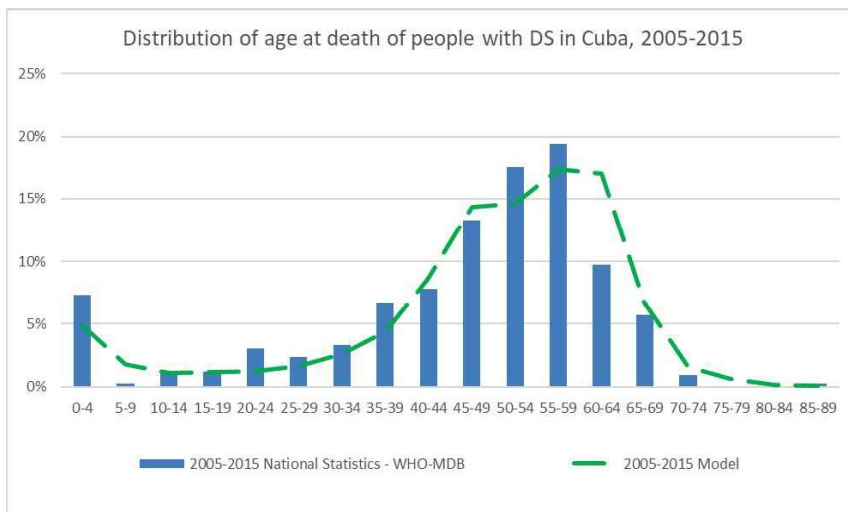
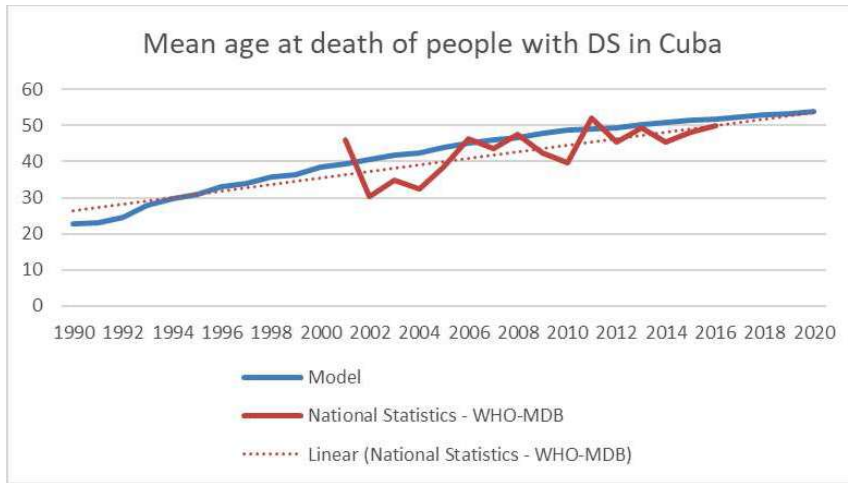
##### *Cayman Islands*

No data on age at death available.

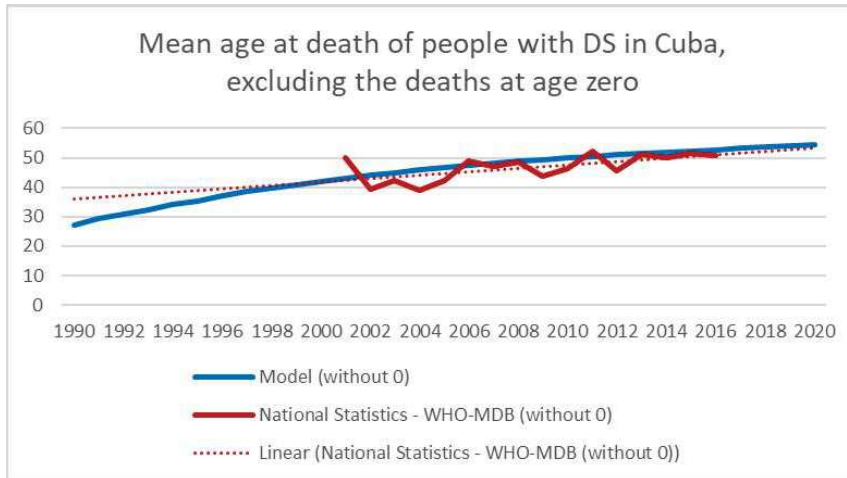
##### *Cuba*

The WHO Mortality Database has data available for 2001–2016, with on average 39 deaths reported

of people with DS as primary cause of death per year. The model predicts on average 76 annual deaths of people with DS in this period; so 51% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are highly similar between model and data.



There is a small discrepancy between the data and the model. An explanation might be that doctors are relatively more often inclined to report Down syndrome as the primary cause of death in very young children. For the figure below, we have excluded from both the data and the model the children who died before 1 year of age. It results in a slightly better fit, so this might be (part of) the explanation.



*Curaçao*

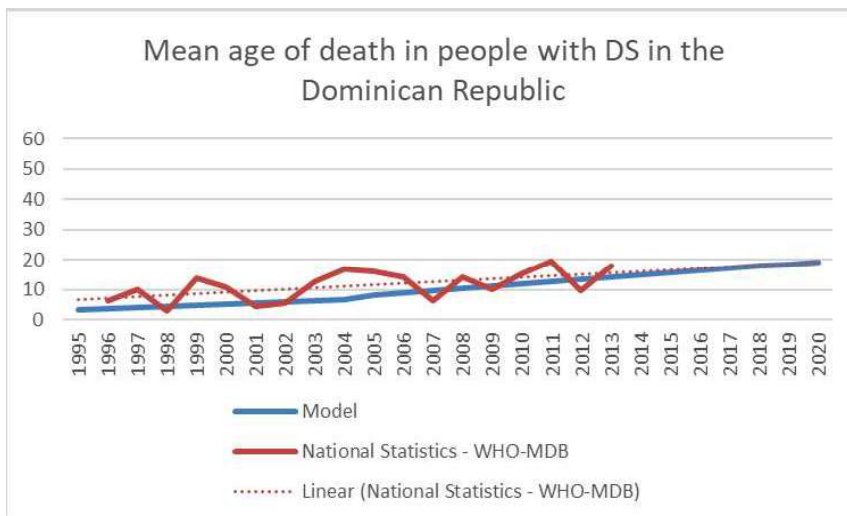
No data on age at death available.

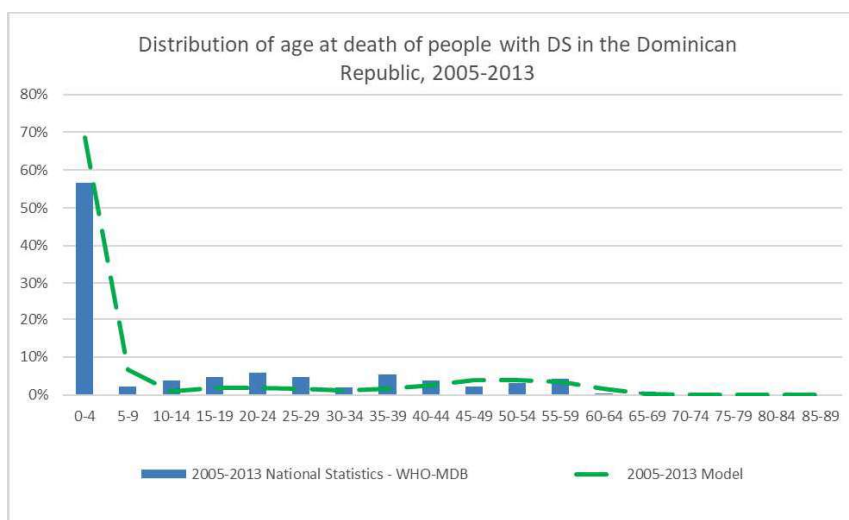
*Dominica*

No data on age at death available.

*Dominican Republic*

The WHO Mortality Database has data available for 1996–2013, with on average 25 deaths reported of people with DS as primary cause of death per year. The model predicts on average 149 annual deaths of people with DS in this period, so 17% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2013) are similar between model and data.





*Grenada*

No data on age at death available.

*Guadeloupe*

Data for only 2000–2001, 2003–2007, 2009–2010, and 2013–2015. And on average 2 deaths per year are reported. Not enough data to make a comparison.

*Haiti*

No data on age at death available.

*Jamaica*

Data for 2000–2006 and 2009–2014, with on average 7 deaths per year reported. Not enough data to make a comparison.

*Martinique*

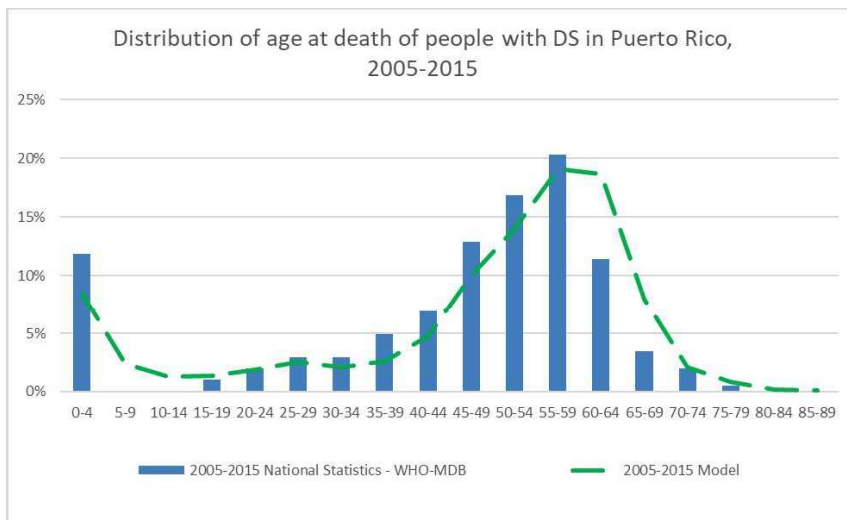
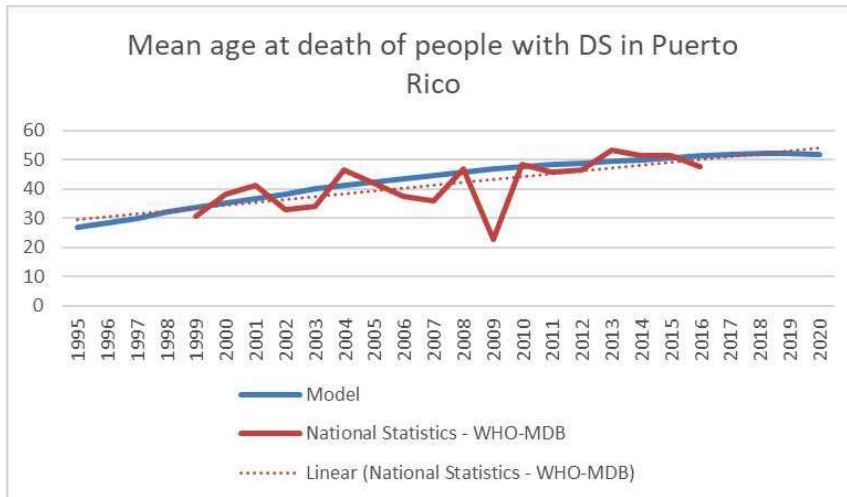
Data for only 2000–2012 and 2014. And on average 2 deaths per year are reported. Not enough data to make a comparison.

*Montserrat*

No data on age at death available.

*Puerto Rico*

The WHO Mortality Database has data available for 1999–2016, with on average 18 deaths reported of people with DS as primary cause of death per year. The model predicts on average 42 annual deaths of people with DS in this period, so 43% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are similar between model and data.



*Saint Barthélemy*

No data on age at death available.

*Saint Kitts and Nevis*

No data on age at death available.

*Saint Lucia*

No data on age at death available.

*Saint Martin (French part)*

No data on age at death available.

*Saint Vincent and the Grenadines*

Data for only 2007, 2010–2011 and 2014. And on average 1 death per year reported. Not enough data to make a comparison.

*Sint Maarten*

No data on age at death available.

*Trinidad and Tobago*

Data for 1999–2012, with on average only 7 deaths per year reported. Not enough data to make a comparison.

*Turks and Caicos Islands*

No data on age at death available.

*United States Virgin Islands*

Data for only 1996, 2006, 2008, and 2010. And on average 1 death per year reported. Not enough data to make a comparison.

**Countries in Central America (and Mexico)**

*Belize*

Data for only 1998–2002 and 2004–2013. And on average 2 deaths per year are reported. Not enough data to make a comparison.

*Costa Rica*

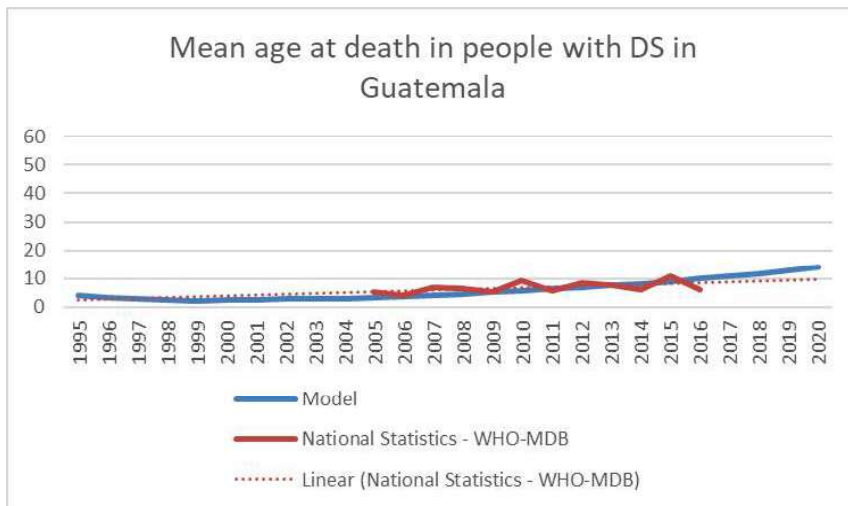
Data for 1997–2014, with on average only 11 deaths per year reported. Not enough data to make a comparison.

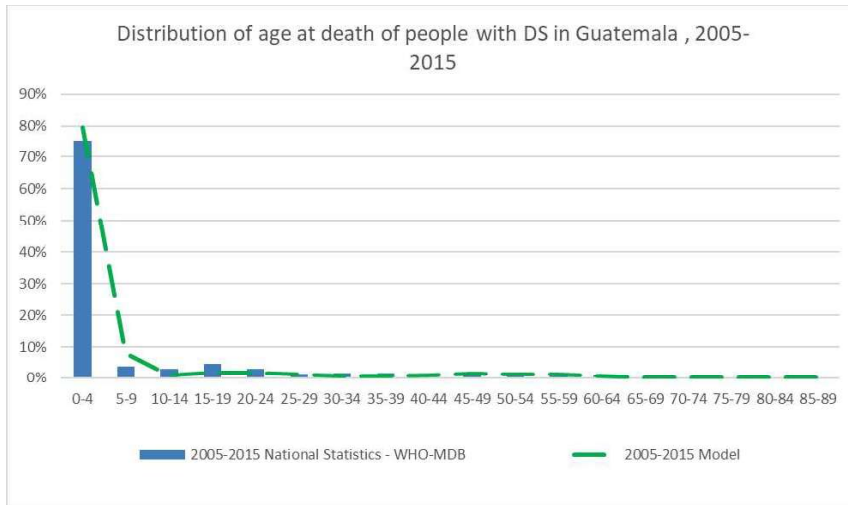
*El Salvador*

Data for only 1997–1998, 2000–2001, and 2003–2014. And on average 5 deaths per year are reported. Not enough data to make a comparison.

*Guatemala*

The WHO Mortality Database has data available for 2005–2016, with on average 76 deaths reported of people with DS as primary cause of death per year. The model predicts on average 393 annual deaths of people with DS in this period, so 19% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are similar between model and data.



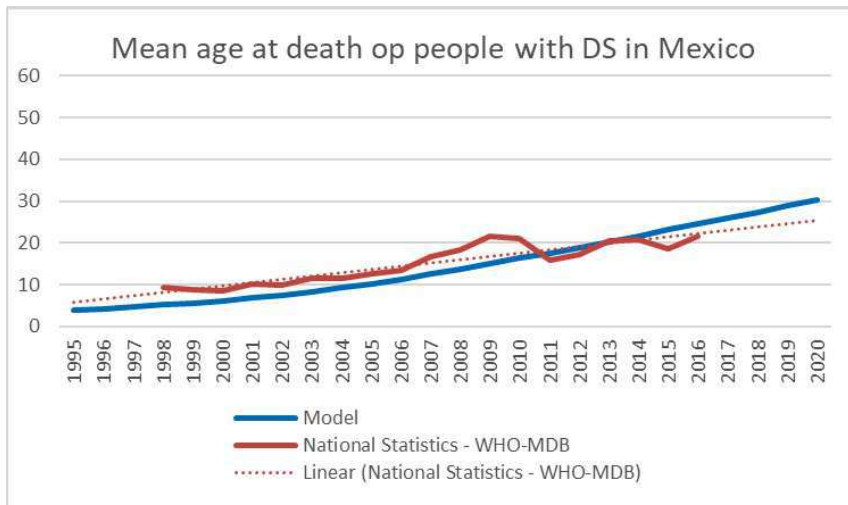


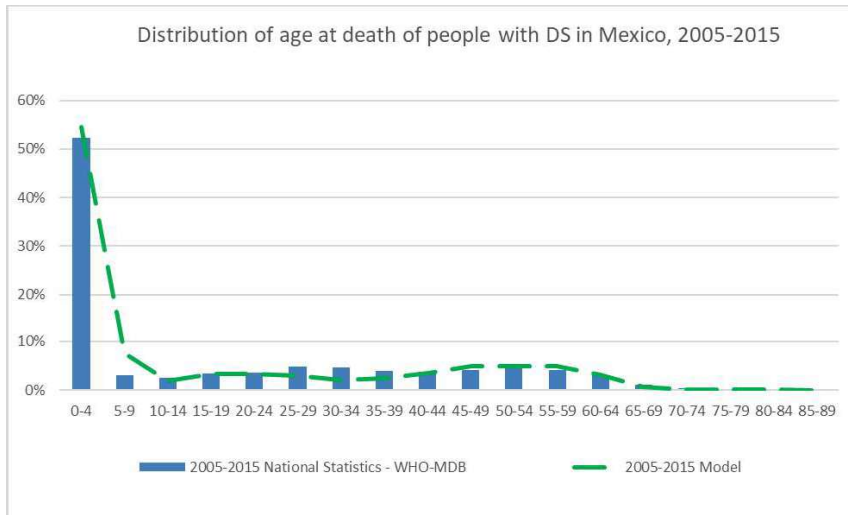
**Honduras**

Data for only 2008–2013. And on average 7 deaths per year are reported. Not enough data to make a comparison.

**Mexico**

The WHO Mortality Database has data available for 1998–2016, with on average 380 deaths reported of people with DS as primary cause of death per year. The model predicts on average 1,313 annual deaths of people with DS in this period, so 29% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are similar between model and data.





**Nicaragua**

Data for 1997–2016, with on average 8 deaths per year reported. Not enough data to make a comparison.

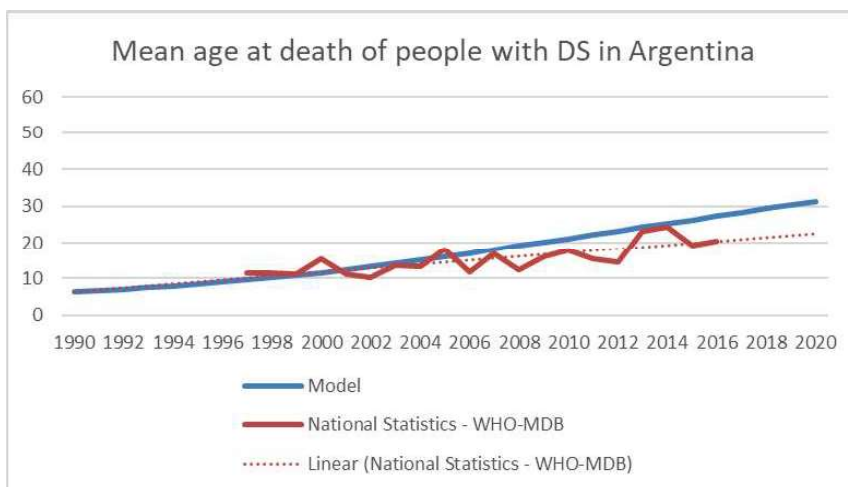
**Panama**

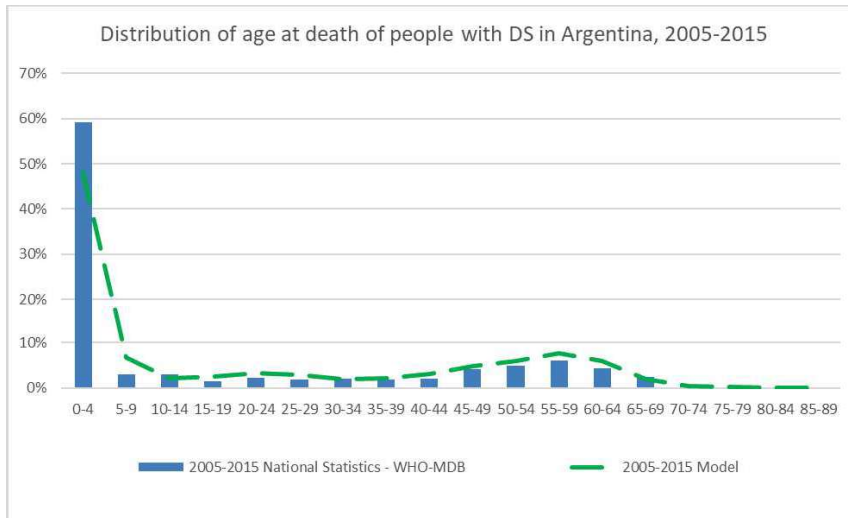
Data for 1998–2016, with on average 7 deaths per year reported. Not enough data to make a comparison.

**Countries in South America**

**Argentina**

The WHO Mortality Database has data available for 1997–2016, with on average 110 deaths reported of people with DS as primary cause of death per year. The model predicts on average 438 annual deaths of people with DS in this period, so 25% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are reasonably similar between model and data.





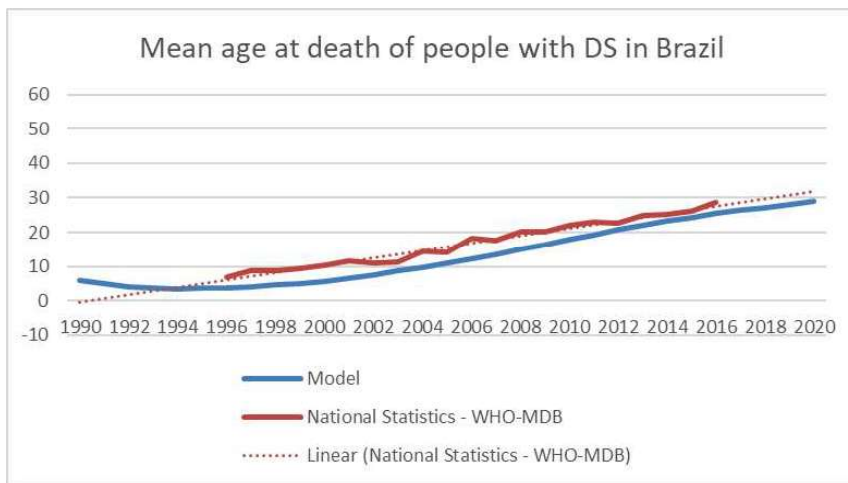
Excluding deaths under 1 year of age does not lead to a better fit.

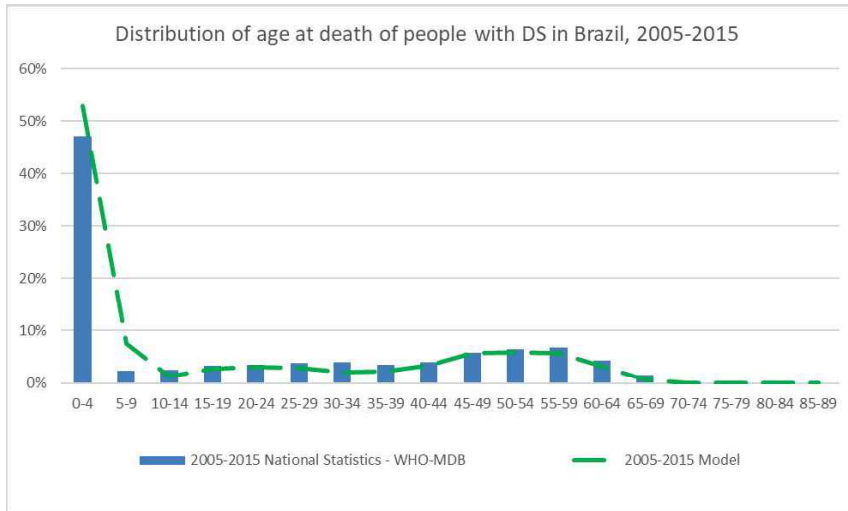
*Bolivia*

No data on age at death available.

*Brazil*

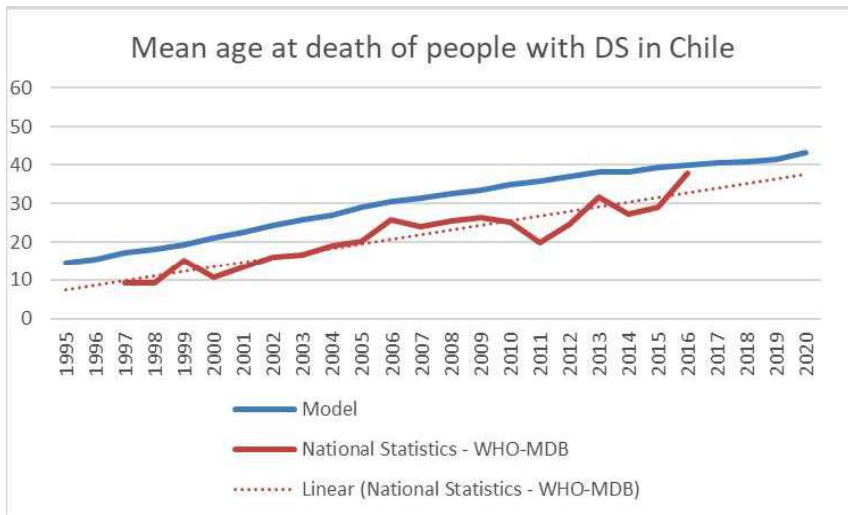
The WHO Mortality Database has data available for 1996–2016, with on average 477 deaths reported of people with DS as primary cause of death per year. The model predicts on average 2,263 annual deaths of people with DS in this period, so 21% is covered in the registration (increasing from 12% at the start of the range of years to 31% at the end). The mean age at death and the distribution of deaths by age group (for 2005–2015) are reasonably similar between model and data.

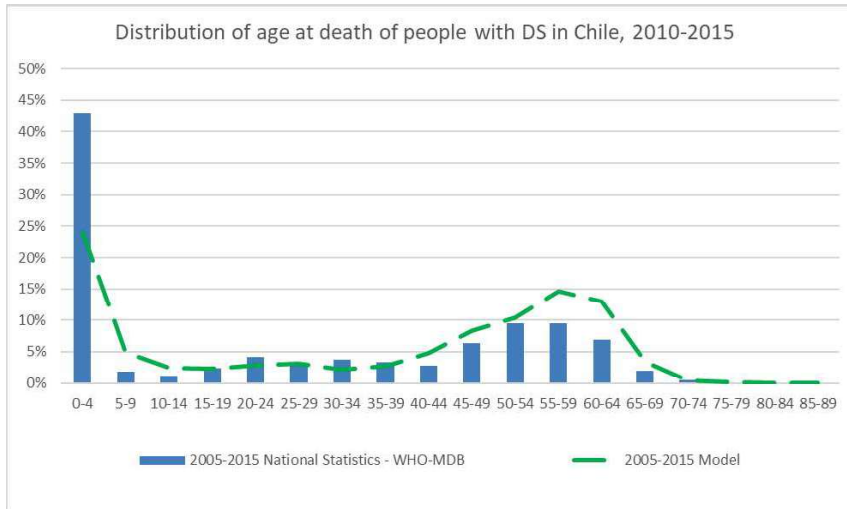




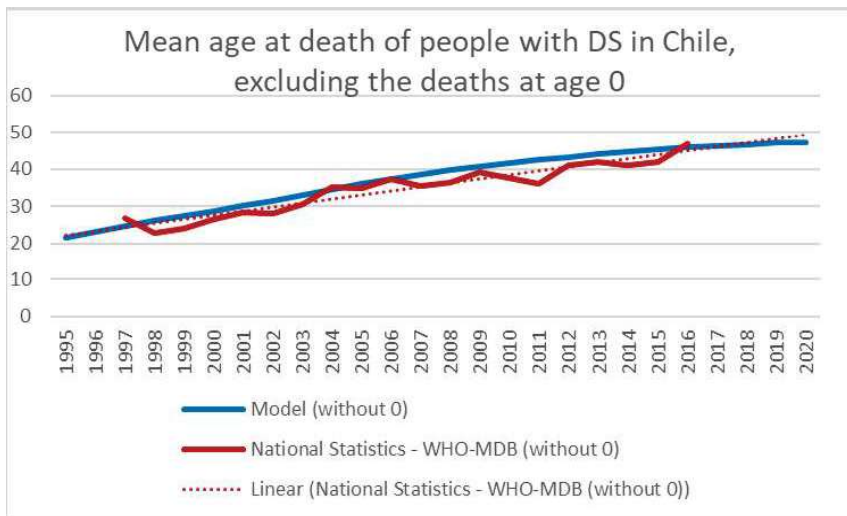
*Chile*

The WHO Mortality Database has data available for 1997–2016, with on average 73 deaths reported of people with DS as primary cause of death per year. The model predicts on average 138 annual deaths of people with DS in this period, so 53% is covered in the registration. The mean age at death, and the distribution of deaths by age group (for 2005–2014) differ between data and model. It appears that the mortality under 10 years of age is estimated too low in the model, with as a result a too low estimate of the number of deaths under 10 years of age.



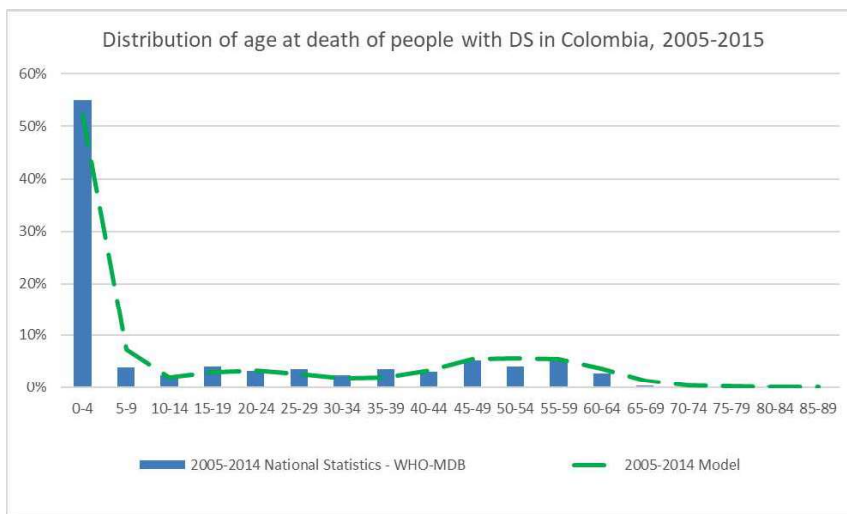
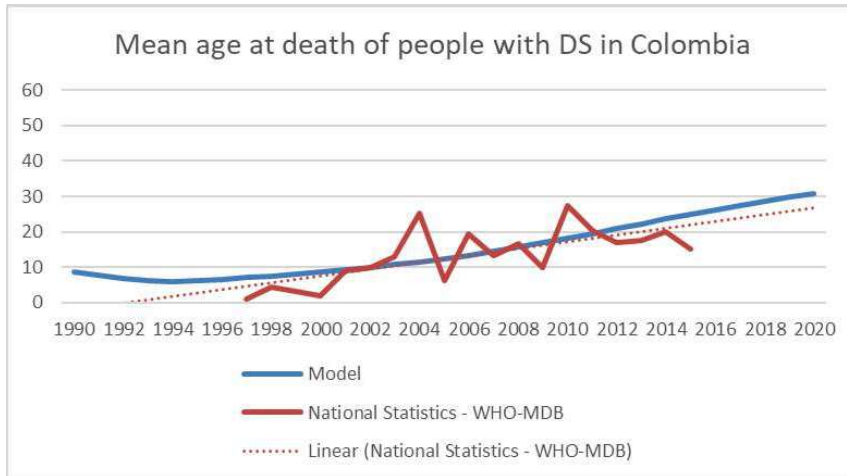


However, another explanation for the discrepancy between data and model might be that doctors are relatively more often inclined to report Down syndrome as the primary cause of death in very young children. For the figure below, we have excluded from both the data and the model the children who died before 1 year of age. It results in a good fit, so this might indeed be the explanation.



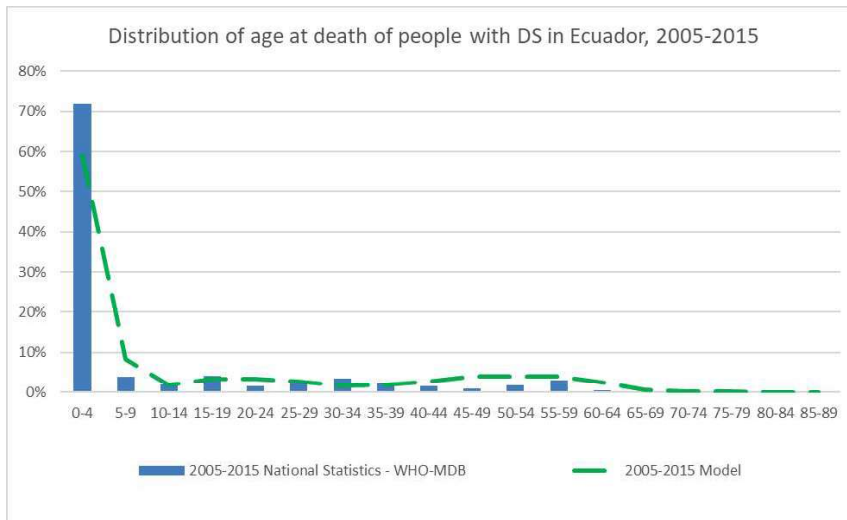
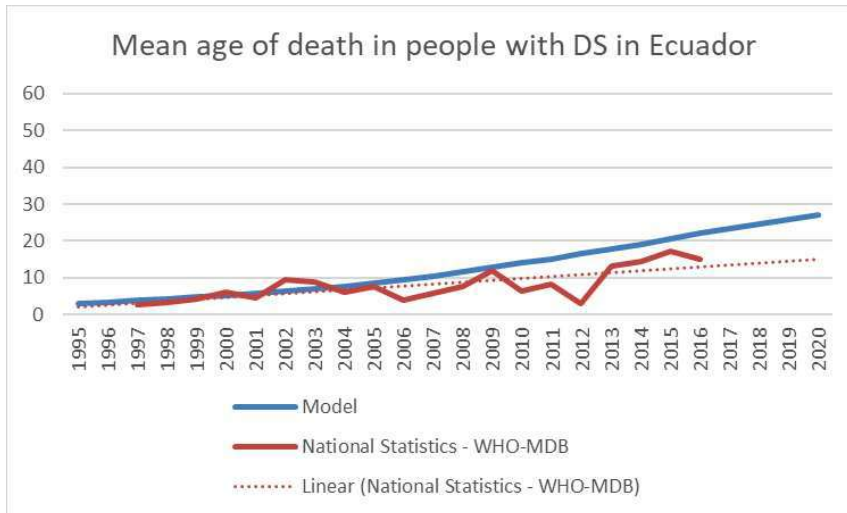
*Colombia*

The WHO Mortality Database has data available for 1997–2015, with on average 29 deaths reported of people with DS as primary cause of death per year. The model predicts on average 522 annual deaths of people with DS in this period, so only 6% is covered in the registration (increasing from 2% in 1997 to 25% in 2015). The mean age at death and the distribution of deaths by age group (for 2005-2015) are similar between model and data.

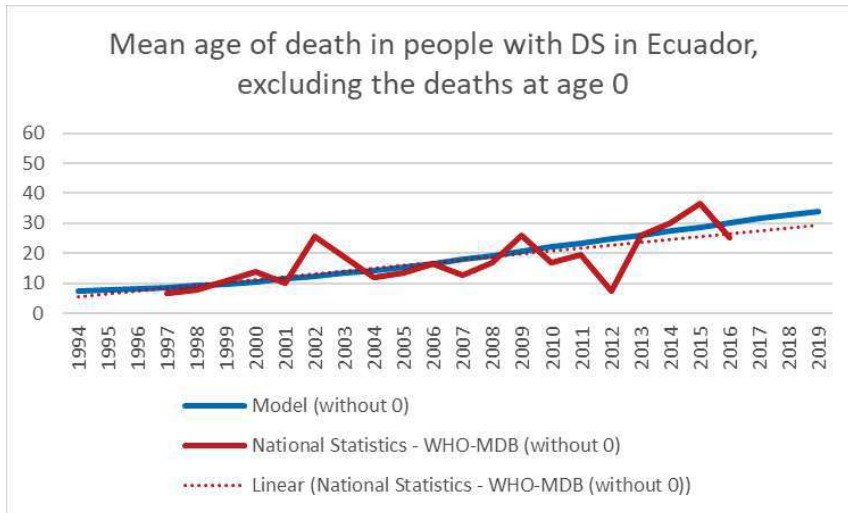


*Ecuador*

The WHO Mortality Database has data available for 1997–2016, with on average 41 deaths reported of people with DS as primary cause of death per year. The model predicts on average 219 annual deaths of people with DS in this period, so 19% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are reasonably similar between model and data. However, the model estimates of the percentage in the youngest group seems to be somewhat higher than in the WHO Mortality Database.



An explanation for the (relatively small) discrepancy between model and data might be that doctors are relatively more often inclined to report Down syndrome as the primary cause of death in very young children. For the figure below, we have excluded from both the data and the model the children who died before 1 year of age. It improves the fit, so this might be (part of) the explanation.



*Falkland Islands*

No data on age at death available.

*French Guiana*

Data for only 2001, 2003, 2005, 2008, 2010–2011, 2015. And on average 1 death (of someone with DS as primary cause of death) per year reported. Not enough data to make a comparison.

*Guyana*

Data for only 2001–2002, 2007–2009, and 2011–2014. And on average 1 death (of someone with DS as primary cause of death) per year reported. Not enough data to make a comparison.

*Paraguay*

The WHO Mortality Database has data available for 1996–1997, 2002–2004, and 2011–2016, with on average 22 deaths reported of people with DS as primary cause of death per year. The model predicts on average 123 annual deaths of people with DS in this period, so 18% is covered in the registration. The mean age at death and the distribution of deaths by age group (for 2005–2015) are similar between model and data.

