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ORIGINAL ARTICLE

After the epidemiologic transition: a reassessment of mortality from infectious diseases among over-65s in France and Italy

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Abstract
Objectives To assess more accurately the contribution of infectious diseases (IDs) to mortality at age 65+.
Methods We use cause-of-death data for France and Italy in 2009. In addition to chapter I of the 10th International Classification of Diseases (ICD-10), our list of IDs includes numerous diseases classified in other chapters. We compute mortality rates considering all death certificate entries (underlying and contributing causes).
Results Mortality rates at age 65+ based on our extended list are more than three times higher than rates based solely on ICD-10 chapter I. IDs are frequently contributing causes of death. In France, the share of deaths at age 65+ involving an ID as underlying cause increases from 2.1 to 7.3 % with the extended list, and to 20.8 % when contributing causes are also considered. For Italy, these percentages are 1.4, 4.2 and 18.7 %, respectively.
Conclusions Publicly available statistics underestimate the contribution of IDs to the over-65s' mortality. Old age is a risk factor for IDs, and these diseases are more difficult to treat at advanced ages. Health policies should develop targeted actions for that population.

Keywords Infectious diseases · Mortality · Multiple causes of death · Aging · Public health

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Introduction

In countries that have completed the second stage of the epidemiologic transition (Omran 1971), the cause-of-death pattern is dominated by cancers and diseases of the circulatory system. Yet, in recent decades, several crises (e.g. HIV, influenza A pandemics and Ebola) have revived the fear of infectious diseases (ID). Regarding the origins of this re-emerging threat, attention focuses mainly on the combined roles of environmental change, socio-economic organization and human behaviour (Durando et al. 2007). Manton and Stallard (1982) prophesized that population aging might result in a fresh upsurge in infectious diseases, since degenerative diseases "often progress to a point where the vitality of the organism as a whole is impaired, at which time the organism is susceptible to a lethal infectious complication". Surprisingly, the relation between infectious diseases and population aging has not received much attention in either the research literature (Suk and Semenza 2011) or the public health policy agenda. A recent analysis of changing mortality patterns in France (Coste et al. 2006) concluded that the conquest of infectious diseases was only partial, notably because these diseases are still a major cause of death in the elderly population. Seniors are not necessarily the prime victims of epidemics, but old age is known to be a risk factor for infectious diseases. Immunosenescence as well as other age-associated anatomical and physiological modifications increase susceptibility to infections that also are frequently more severe and more difficult to treat (Gavazzi and Krause 2002; Remais et al. 2013).

In France and Italy, the two countries examined in this paper, four in five deaths from a cause listed in chapter I ("certain infectious and parasitic diseases") of the 10th revision of the International Classification of Diseases

(ICD-10) concern people aged 65 and older. Our premise is that publicly available figures underestimate the contribution of infectious diseases to mortality. Firstly, ICD-10 chapter I does not include all infectious diseases. Many of them (i.e. influenza and pneumonia) are classified in other chapters. Secondly, these figures are based exclusively on the underlying cause (UC) of death. The World Health Organization (WHO) defines the underlying cause as the disease "which initiated the train of morbid events leading directly to death". As the situation described by Manton and Stallard suggests, infectious diseases may often be involved in the process leading to death as a complication of another cause. Under the WHO coding rules, in this case, the infectious disease will not be selected as the underlying cause of death.

In the analysis presented in this paper, these two sources of underestimation of ID mortality are taken into account. We first recalculate underlying-cause mortality levels using a list of infectious diseases that is not restricted to ICD-10 chapter I. Then we compute indicators that take into account all death certificate entries (multiple causes). Our approach is known as multiple cause-of-death (MCOD) analysis. It has been used for a wide range of diseases (Désesquelles et al. 2012) but very few studies have focused on infectious diseases. Our study follows on from Pinner's (1996) analysis of trends in infectious mortality in the US between 1980 and 1992 which, despite several differences in method, had similar aims. We examine how frequently infectious diseases are selected as the underlying cause, and we evaluate mortality levels based on all death certificate entries.

Methods

Data

Data for the two countries are for 2009. They are produced by the Italian National Vital Statistics Death Registry on causes of death, managed by the Italian National Institute of Statistics (ISTAT), and by the statistics of the medical causes of death, managed by the French National Institute for Health and Medical Research (INSERM). Data are based on the information reported on the death certificates. In line with WHO recommendations, French and Italian death certificates comprise two parts. On part I, designed to elicit the underlying cause of death, the certifying physician reports the morbid process that directly led to death, from the immediate cause of the death to the initial cause that started the sequence. Part II is for "any other significant condition that unfavourably influenced the course of the morbid process but is not related to the condition directly causing death". In both countries, there is no restriction in the number of causes coded and recorded in the databases, and multiple causes of death are coded under ICD-10. In this study, we use all the causes reported by the certifying physicians, in both part I and part II. We call contributing causes (CC) all causes others than the UC reported by the certifying physicians on either part I or II. The databases at our disposal include all deaths that occurred in France and Italy, but for the purpose of this study, analysis is restricted to deaths at age 65 and over.

List of causes

We use an extended list of infectious diseases that comprises 16 subgroups (see "Appendix"). In addition to ICD-10 chapter I divided into six subgroups ("tuberculosis", "AIDS (HIV disease)", "viral hepatitis", "septicaemia", "intestinal infectious diseases" and "other infectious and parasitic diseases of chapter I"), we include influenza and pneumonia that are classified with the diseases of the respiratory system as well as all infectious diseases classified in other ICD-10 chapters. In particular, we select all entries containing one of these terms: infection, infectious agent, abscess, gangrene and fever. We also select all ICD-10 subcategories that, in most cases, have an infectious origin. As an example, inflammatory disorders are generally due to an infectious agent. The selected codes are grouped under the chapter to which they belong. Chapter IX is for circulatory system, X for respiratory system, XI for digestive system, XII for skin and subcutaneous tissue, XIII for musculoskeletal system and connective tissue, XIV for genitourinary system, and XVIII for ill-defined causes. A residual subgroup includes all infectious diseases of the other ICD-10 chapters (chapters III, IV, VII and VIII). Chapter III is for "Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism", chapter IV for "Endocrine, nutritional and metabolic diseases", chapter VII for "Diseases of the eye and adnexa", and chapter VIII for "Diseases of the ear and mastoid process".

Indicators

We first compute age- and sex-standardized mortality rates. For the underlying-cause mortality rate, only entries selected as UC are considered. For the multiple-cause mortality rate, we consider all entries on the death certificates and, for every subgroup of our list, we calculate how many deaths have at least one entry belonging to that subgroup. Let M_{uc} and M_{mc} be the standardized underlying and multiple cause-of-death mortality rates for a specific subgroup of causes. We have:

$$M_{\text{uc}} = \frac{\sum_x \frac{d_{u,x}}{P_x} \cdot Ps_x}{\sum_x Ps_x} \text{ and } M_{\text{mc}} = \frac{\sum_x \frac{d_{m,x}}{P_x} \cdot Ps_x}{\sum_x Ps_x}$$

where $d_{u,x}$ is the number of deaths at age x with an entry in a specific subgroup as underlying cause, $d_{m,x}$ is the number of deaths at age x with at least one entry in a specific subgroup as multiple cause, P_x is the average population size at age x, Ps_x is the standard population size at age x. The standard population is the Eurostat 2013 European population by sex and 5-year age groups.

The standardized ratio of multiple to underlying cause (SRMU) is defined as the ratio between the standardized multiple-cause and the standardized underlying-cause mortality rates (Désesquelles et al. 2012). Hence,

$$\text{SRMU} = \frac{M_{\text{mc}}}{M_{\text{uc}}} = \frac{\frac{\sum_x \frac{d_{m,x}}{P_x} Ps_x}{\sum_x Ps_x}}{\frac{\sum_x \frac{d_{u,x}}{P_x} Ps_x}{\sum_x Ps_x}}$$

The SRMU is close to one for conditions that are usually selected as the underlying cause and above one for conditions that are less frequently selected as such. Assuming that the observed number of deaths follows a Poisson distribution, 95 % confidence intervals were computed for both the mortality rates and the SRMUs. All differences between the two countries are significant, and all SRMU values are significantly over one. All the statistical analyses were performed using SAS 9.3.

Results

In 2009, among 427,222 deaths in France and 509,428 deaths in Italy of people aged 65 and over, 8600 deaths in France and 7000 deaths in Italy were attributed to an infectious disease of ICD-10 chapter I. When restricted to these codes (Table 1), the standardized underlying-cause mortality rate at age 65 and over is 82 per 100,000 in France and 59 per 100,000 in Italy. Rates are higher in France than in Italy for "intestinal infectious diseases" (12 vs. 3 per 100,000) and for "other infectious and parasitic diseases of chapter I" (25 vs. 6 per 100,000). Conversely, they are higher in Italy than in France for viral hepatitis (17 vs. 3 per 100,000). In both countries, the highest rates are for septicaemia (35 per 100,000 in France and 30 per 100,000 in Italy).

In 2009, 31,296 deaths in France and 21,296 deaths in Italy among over-65s were attributed to an infectious disease of our extended list. When based on this list, the underlying-cause mortality rates are multiplied by 3.6 in France (from 82 to 298 per 100,000) and by 3.1 (from 59 to 185 per 100,000) in Italy. In both countries, half of the observed increase is due to pneumonia, the leading cause of infectious mortality (105 per 100,000 in France and 64 per 100,000 in Italy). But several other subgroups (e.g. other infections of the respiratory system, infectious diseases of the circulatory, digestive and genitourinary systems and, to lesser extent, of the skin and the subcutaneous tissue) contribute significantly to the upward revision.

The use of the extended list increases the French disadvantage in terms of ID mortality. Among all additional subgroups, the mortality differential between the two countries is especially high for pneumonia but we find a French disadvantage for several other subgroups whose contribution to mortality is more modest (e.g. infectious diseases of the circulatory, respiratory and genitourinary systems, as well as infectious diseases of the skin and subcutaneous tissue).

In 2009, among over-65s, 88,696 death certificates in France and 95,506 death certificates in Italy had at least one entry of an ID in our extended list as multiple cause. The average number of reported causes on those certificates is 3.9 in Italy and 3.3 in France. In both countries, the standardized ratio of multiple to underlying cause (SRMU) is close to one for AIDS (1.2 in France and 1.3 in Italy) and for influenza (1.1 in France and 1.3 in Italy): when reported on death certificates, these diseases are generally selected as the underlying cause. The highest SRMUs are for infectious diseases of the skin, for ill-defined infectious diseases, and for septicaemia (6.0 in France and 7.1 Italy). In other words, more than five in six entries of septicaemia are not the UC. The MCOD approach leads to a remarkable upward revision of the role played by infectious diseases of the skin (mainly decubitus ulcer) in mortality.

Almost all other SRMUs are over 2, and they are generally higher in Italy than in France. This is the case, for instance, for pneumonia (3.4 in France and 5.4 in Italy). As a consequence, when considering all entries on the death certificates, the differential between the two countries in terms of pneumonia mortality almost disappears (352 per 100,000 in France and 343 per 100,000 in Italy). This also applies for infectious diseases of the circulatory and the genitourinary systems. For intestinal infectious diseases and for "other infectious diseases of the respiratory system", the French disadvantage decreases, while for infectious diseases of the skin, the situation is reversed: the multiple-cause mortality rate becomes higher in Italy (75 per 100,000 vs 68 per 100,000 in France). SRMUs are similar in the two countries for viral hepatitis (3.3 in France and 3.1 in Italy), so the MCOD approach does not affect the Italian disadvantage in terms of mortality from this disease.

In all, in France, the share of deaths from an infectious or parasitic disease at ages 65 and over increases from 2.1 to 7.3 % when the extended list is used and to 20.8 % when

Table 1 Standardized mortality rates (per 100,000) based on the underlying cause and multiple causes, and standardized ratio of multiple to underlying cause (SRMU)

Cause of death	Standardized rates based on the underlying cause (1)		Standardized rates based on multiple causes (2)		Standardized ratio of multiple to underlying cause (1)/(2)	
	France	Italy	France	Italy	France	Italy
Tuberculosis	5	3	11	8	2.1	2.8
AIDS (HIV disease)	1	1	1	1	1.2	1.3
Viral hepatitis	3	17	11	53	3.3	3.1
Septicaemia	35	30	209	212	6.0	7.1
Intestinal infectious diseases	12	3	17	6	1.4	2.1
Other diseases of chapter I	25	6	99	21	3.9	3.7
All diseases of ICD-10 chapter I	82	59	330[a]	290[a]	4.0	4.9
IDs of chapter IX (circulatory)	20	12	57	54	2.9	4.3
Influenza	3	4	3	5	1.1	1.3
Pneumonia	105	64	352	343	3.4	5.4
Other IDs of chapter X (respiratory)	32	11	83	43	2.6	3.9
IDs of chapter XI (digestive)	20	18	45	48	2.2	2.7
IDs of chapter XII (skin)	11	5	68	75	6.2	>10
IDs of chapter XIII (musculoskeletal)	3	1	6	2	1.9	2.6
IDs of chapter XIV (genitourinary)	20	8	51	49	2.5	5.8
IDs of chapter XVIII (ill-defined)	1	1	28	78	>10	>10
IDs of chapters III, IV, VII, and VIII	2	2	5	5	2.2	2.2
Extended list of infectious diseases	298	185	854[a]	830[a]	2.9	4.5
All causes of death	4052	4341	–	–	–	–

Deaths at age 65+, France and Italy, 2009

The standard population is the Eurostat 2013 European population

Data: France: INSERM CépiDc mortality database/Italy: ISTAT mortality database

[a] MC rates are not additive. A given death record may have one subgroup in the list as underlying cause and another subgroup in the list as contributing cause

the contributing causes are also considered. For Italy, these percentages are 1.4, 4.2 and 18.7 %, respectively.

Discussion

The two sources of underestimation examined in this paper strongly affect measurements of ID mortality.

First, mortality rates at age 65 and over based on ICD-10 chapter I are more than three times lower than the rates based on our extended list. It is difficult to compare our results with other studies because they differ from ours in several respects (time period, age group, ICD classification, list of IDs). The aforementioned study for the US in 1992 (Pinner et al. 1996) found a less pronounced underestimation. Deaths at all ages with an underlying cause in ICD-10 chapter I represented 40 % of the number of ID deaths identified with an extended list. But at that time, the burden of AIDS-related deaths, which are categorized in ICD-10 chapter I, was very high. In a more recent study for Italy, Angeletti (Angeletti et al. 2004) found a very similar result as Pinner for the period 1990–1999 even though he had excluded AIDS-related deaths from his measurement.

Secondly, infectious diseases are very frequently not selected as the underlying cause of death. The most striking examples are septicaemia and pneumonia, whose contribution to mortality is considerably underestimated when the UC only is considered. There are several ways in which infectious diseases may contribute to the lethal process (Désesquelles et al. 2014): (1) the ID is a consequence or a complication of the underlying cause or its treatment. Immunosuppression due to chemotherapy or bed confinement due to injury or disease may result in infections; (2) the ID is a risk factor for the underlying cause. For example, chronic viral hepatitis C is a risk factor for liver cancer; (3) the ID and the underlying cause have a common cause (e.g. intravenous drug use as a common cause for hepatitis C and overdose); (4) the ID is a "background" factor (Manton and Stallard 1982) for the underlying cause: the combination of the underlying cause and the contributing cause results in increased risk of dying, reflecting either synergistic or additive processes. Typically, chronic

Table 2 Among the death records with a specific subgroup of infectious diseases as contributing cause, proportion of the deaths with another subgroup of infectious diseases as underlying cause

Contributing infectious disease	% with another infectious disease as underlying cause	
	France (%)	Italy (%)
Tuberculosis	7	4
AIDS (HIV disease)	0	1
Viral hepatitis	6	3
Septicaemia	26	16
Intestinal infectious diseases	11	11
Other diseases of chapter I	17	11
IDs of chapter IX (circulatory)	7	4
Influenza	4	0
Pneumonia	5	4
Other IDs of chapter X (respiratory)	4	3
IDs of chapter XI (digestive)	4	4
IDs of chapter XII (skin)	10	6
IDs of chapter XIII (musculoskeletal)	18	11
IDs of chapter XIV (genitourinary)	11	6
IDs of chapter XVIII (ill-defined)	13	10
IDs of chapters III, IV, VII, and VIII	16	17
Extended list of IDs	13[a]	8[a]

Deaths at age 65+, France and Italy, 2009

Interpretation: in France, for 7 % of deaths at age 65+ with tuberculosis as contributing cause, the underlying cause is an infectious disease of another subgroup in our list

Data: France: INSERM CépiDc mortality database/Italy: ISTAT mortality database

[a] These figures include cases where the underlying and the contributing causes belong to the same subgroup in our list

infections like HIV or hepatitis may play such a role in morbid processes.

Here, it must be noted that infectious diseases may contribute to deaths whose underlying cause is also an infectious disease. Around one in ten deaths at age 65 or over with an ID as contributing cause has an infectious disease as underlying cause. Table 2 shows these proportions for the detailed subgroups of our list. For many subgroups, less than 10 % of the deaths have an ID as underlying cause. This situation is more frequent for septicaemia (26 % in France and 16 % in Italy), for our residual subgroup of infectious diseases (16 % in France and 17 % in Italy) and, specifically to France, for "other infectious and parasitic diseases of chapter I" (17 %) and infectious diseases of the musculoskeletal system (18 %).

Interestingly, our analysis also sheds light on differences between the two countries in terms of ID mortality when the underlying cause only is considered. Common interpretations for such differences involve differences in disease prevalence or lethality. For example, the Italian disadvantage in terms of viral hepatitis mortality can be interpreted in light of epidemiological data suggesting that the prevalence of hepatitis B and C in Europe varies geographically along a north–south gradient, with higher prevalence in Mediterranean areas (Hahné et al. 2013). For pneumonia, intestinal infectious diseases and infectious diseases of chapters X, XII and XIV, we cannot exclude that the French disadvantage reflects higher disease prevalence or lethality. However, the fact that corresponding SRMUs are higher in Italy possibly reveals that these diseases are more frequently involved in the process leading to death as consequences of the underlying cause in Italy than in France.

Limitations

Most critics about the MCOD approach focus on the data quality. The quality of multiple cause-of-death data depends on both certification and coding (Mackenbach et al. 1995; Désesquelles et al. 2012). Both France and Italy use the same automated coding system (Automated Classification of Medical Entities or ACME) to select the UC but they use different systems to code multiple causes. While the French system—STYX (Pavillon et al. 2005)—directly produces ICD-10 codes, the Italian one—COD-SAN II (ISTAT 2004)—uses the USA-ERN (Entity Reference Number) system that translates each medical term into a number. A transition table is then used to convert the ERN into an ICD-10 code. As we use an aggregated list of causes, we do not expect any significant impact on the results presented in this paper.

Regarding the information provided by the certifying physicians, they may report diseases that were present at death but did not contribute to the morbid process; conversely, they may omit certain diseases that contributed to the death. In the case of life-threatening infectious diseases, we are confident that certification is rarely inaccurate, because these infections are well known and quite easy to diagnose. For less serious IDs, both over and under-reporting may occur. Comparison of the average number of reported causes in both countries indicates that Italian certifying physicians report more conditions than their French counterparts (Désesquelles et al. 2012). The different format of the French and the Italian death certificates—the French certificate has 6 lines (4 in part I, 2 in part II) while the Italian certificate has 13 lines (8 in part I, 5 in part II)—probably contributes to this situation, which obviously results in higher SRMUs in Italy. All in all, the overall upward reassessment of ID mortality is of similar extent in both countries, however, and these observations do not challenge our general conclusion that publicly available statistics underestimate the contribution of infectious diseases to mortality.

The list of infectious diseases we use is specific to our study. Unfortunately, there is no internationally validated list that we might use instead. It is worth noting that our extended list was established under medical supervision. We could not use the same list as Pinner (Pinner et al. 1996) because it is based on ICD-9. But following his logic, we included all diseases that have an infectious origin "in essentially all cases". Apart from this exception, we adopted a conservative strategy. As an example, a more exhaustive list might include certain neoplasms (cervix uteri, gastric, nasopharyngeal) that are known to have an infectious origin (human papillomavirus, helicobacter pylori, Epstein–Barr virus, respectively) (De Martel et al. 2012). The final impact of our choices on the upward revision of ID-related mortality cannot be evaluated. We, therefore, strongly recommend that the WHO coordinates work to define an extended list of infectious diseases.

Implications of our research

Our research has several public health implications. In terms of monitoring, it shows that published ID mortality rates should not be restricted to ICD-10 chapter I but should also include infectious diseases classified with the organ system diseases. Our research also strongly supports the use of the multiple cause-of-death approach, along with the underlying-cause approach. The method is especially valuable in countries with aging populations, where multimorbidity will be a growing public health concern. As far as infectious diseases are concerned, given that they very frequently play a role in the death of older adults, either directly or indirectly, health policies should foster the use of available prevention strategies in that population and develop more targeted actions.

Conflict of interest None declared.

Appendix

See Table 3.

Table 3 ICD-10 codes of the extended list of infectious and parasitic diseases

Tuberculosis	A15–A19, B90
AIDS (HIV disease)	B20–B24
Viral hepatitis	B15–B19, B94.2
Septicaemia	A40–A41
Intestinal infectious diseases	A00–A09
Other diseases of chapter I	(A00–B99)—Supra codes + (U01–U49 + U80–U89)
IDs of chapter IX (circulatory) (example: endocarditis)	I00–I02, I30.1, I30.9, I33, I38, I40.0, I80
Influenza	J09–J11
Pneumonia	J12–J18
Other IDs of chapter X (respiratory) Example: acute respiratory infections	J00–J06, J20–J22, J31–J32, J34.0, J36–J37, J39.0, J39.1, J40–J41, J85–J86
IDs of chapter XI (digestive) Example: Peritonitis	K02, K04, K05.0–K05.3, K10.2, K11.3, K12, K14.0–K14.2, K20, K35–K37, K40.1, K40.4, K41.1, K41.4, K42.1, K43.1, K44.1, K45.1, K57.8, K46.1, K57.0, K57.2, K57.4, K61, K63.0, K75.0, K65, K81, K85
IDs of chapter XII (skin) Example: decubitus ulcer	L04, L00–L08, L88–L89
IDs of chapter XIII (musculoskeletal) Example: osteomyelitis	M00, M02, M60.0, M65.0–M65.1, M71.0–M71.1, M86
IDs of chapter XIV (genitourinary) Example: urinary tract infection	N10–N12, N13.6, N15, N30, N34, N39.0, N41, N43.1, N45, N48.1–N48.2, N49, N61, N70–N73, N75–N76
IDs of chapter XVIII (ill-defined) Example: gangrene	R02, R50.8, R50.9, R56.0, R75, R82.7
IDs of chapters III, IV, VII, and VIII Example: bacterial meningitis not elsewhere classified	D733, E06.0, E06.1, G00, G04, G06, G08, G09, G61, H00, H01.0, H01.8, H01.9, H04.3, H05.0, H10, H16, H20, H30, H44.0, H44.1, H46, H60.0–H60.3, H60.8, H60.9, H65.0–H65.3, H66, H68.0, H70, H73.0

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