

Pathogens provoking most deaths worldwide: A review

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ABSTRACT

A list of the globally most important pathogens is generated based on the causes of death statistics published in the Global Burden Disease study 2015. Pathogens are assigned to the specified diseases as far as possible. Difficulties arise because the death provoking pathogens are often unidentified or arise in mixed infections with more than one pathogenic agent. Furthermore it is possible that a single causative microorganism is involved in different diseases. For 1.1 of 8.8 million casualties in 2015 no provoking pathogen could be assigned. The identified pathogens that are assumed to cause more than 5 000 deaths annually are specified. The resulting list starts with *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Human immunodeficiency virus* and *Plasmodium falciparum*. Together they are responsible for an estimated 4.7 million casualties which is more than 50% of all deaths provoked by pathogenic agents in 2015.

KEY WORDS: FATAL PATHOGENS, HI-VIRUS, MYCOBACTERIUM TUBERCULOSIS, PLASMODIUM FALCIPARUM, STREPTOCOCCUS PNEUMONIAE

INTRODUCTION

Knowledge of the most important diseases is essential for the advancement of public health but sometimes it is still not enough. At least for infectious diseases often a more precise information about the major responsible pathogens is required for future development of medical prevention measures, like vaccination, or disinfection techniques for water, air and food. Every few years the Institute for Health Metrics and Evaluation (IHME) publishes a new version of the Global Burden Disease study

(GBD) with a vast amount of information on the global health situation. Among this data statistics of cause-specific mortality can be found, including the number of deaths caused by different infections that totals almost 9 million casualties (Wang et al., 2016a). The danger of premature death is significantly higher in the developing world than in the industrialized countries and according to the data, children under the age of 5 are particularly at risk.

These data are not general knowledge, even among health professionals. Due to vast changes in the last

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decade caused by effective sanitary and medical measures like vaccination programs, the worldwide situation and therefore the death statistics underwent distinct alteration. Another reason is the large amount of existing data that impedes the possibility to simply gather an overview. Lastly the data provided by different organizations within the last few years seems to be slightly contradictory. The numbers of the UN / Unesco (United Nations, 2013) give the impression that every 20 seconds a child below 5 years dies of diarrhea caused by contaminated water which would result in almost 1.6 million dead children per year and would make diarrhea the globally most important disease. In another wording UN Secretary General Ban Ki-moon talked about more than 800 000 children annually dying of diarrhea (UN Secretary-General, 2013) which would still make it the most important disease at least for children below 5 years.

These numbers, that can be found in official brochures and speeches, are difficult to retrace and they are in contrast to lower values in the Global Burden Disease study 2010 (Liu et al., 2012) and the even more lower numbers in the Global Burden Disease studies of 2013 (Murray et al., 2015) and 2015 (Wang et al., 2016a). This mentioned GBD 2015 study is not only newest but it is also much more detailed and better documented than the UN documents and has passed quality criteria like peer review processes. In conclusion the GBD 2015 study is most probably the most reliable data source on causes of death for infections and other diseases.

Due to enhanced medical treatment, including vaccination and improved sanitation and drinking water supply the number of casualties – published in the different Global Disease Studies – has fortunately decreased for many causes of death within the last decade. To continue this positive development more information on the causes of death would be helpful. Concerning diseases this means identifying the provoking pathogens. For some infections caused by a known single microorganism this does not represent a problem, but among the most important illnesses like diarrhea and lower respiratory tract infections there are many potential pathogens generating similar symptoms and sometimes even co-infections caused by more than one pathogen occur.

The importance of this knowledge is self-evident for medical treatment like the prescription of antibiotics. But it is also crucial for technical developments like the application of UV-C water disinfection for diarrhea prevention in the Developing Countries, one of the topics of our working group (Hessling et al., 2016). Diarrhea could be provoked by bacteria like *Vibrio cholerae* or *Escherichia coli* or viruses like *rotavirus* or *adenovirus*. To reduce the concentration of *Vibrio cholerae*

by three orders of magnitude a UV-C irradiation dose of about 2.2 J/cm² would be necessary. To achieve the same result for *Escherichia coli* 5 – 10 J/cm² are required and for *rotavirus* or *adenovirus* it would be even 25 J/cm² and 100 J/cm², respectively (Chevrefils and Caron, 2006). This clearly shows that not only medication but also technical developments would actually benefit from knowing the most important pathogens.

MATERIAL AND METHODS

The imaginable approach to create a listing of pathogens and their number of global casualties by looking for all known pathogens and count the deaths they provoked is almost impossible because of two reasons: 1.) There is the large number of 1400 known human pathogenic species (*Nature Reviews Microbiology*, 2011) and 2.) information on the number of deaths doesn't globally exist for most of them.

Fortunately there is the Global Burden Disease Study 2015 with information on the world wide health situation compiled, evaluated and analyzed by a large number of experts. Among the provided data are statistics on the global numbers of deaths caused by different diseases (Wang et al., 2016a). The values are rather estimations than exact indications but nevertheless probably the most accurate, current available numbers and therefore they are taken as fixed basis for this investigation. As far as necessary and possible missing data is supplemented by studies published within the last 10 years.

In a first step all diseases mentioned in (Wang et al., 2016a), that are provoked by at least one pathogen are identified and in a second step the responsible pathogens and their assumed share of casualties is elaborated (Table 1). This is not always straight forward, because of complications like incomplete data and due to co-infections by more than one pathogen.

TUBERCULOSIS AND AIDS

Tuberculosis and AIDS are among the most widespread infectious diseases with loss of life result. Tuberculosis is caused by *Mycobacterium tuberculosis* and is responsible for more than 1.1 million deaths in 2015. AIDS claimed almost 1.2 million casualties in the same period (Wang et al., 2016a), but the explicit assignment to a specific pathogen is somewhat more complex compared to Tuberculosis. AIDS is provoked by the *HI-virus* but the patients die because of co-infections like tuberculosis or pneumoniae or other diseases. Nevertheless the GBD 2015 study assigns these casualties to AIDS and this procedure is continued here, wherefore these deaths are assigned to the *HI-virus*.

Table 1. Diseases listed in GBD 2015, with number of casualties and responsible pathogens and their estimated share of cases of deaths.					
Disease	Total casualties [Thousands]	Pathogen(s)	Estimated share [%]	Estimated casualties [Thousands]	Reference / Remark
Lower respiratory infections	2736.7				(Wang et al., 2016a)
Pneumococcal pneumonia		<i>Streptococcus pneumoniae</i>	55.4	1516.1	(Wang et al., 2016b)
Mycoplasma pneumonia		<i>Mycoplasma pneumoniae</i>	10	273.7	(Arnold et al., 2007; Cilloniz and Torres Antonio, 2016; Loebinger and Wilson, 2012) (mean value)
Legionnaires' disease		<i>Legionella spp.</i>	5.3	145.0	(Arnold et al., 2007; Cilloniz and Torres Antonio, 2016; Loebinger and Wilson, 2012) (mean value)
Influenza		<i>Influenza virus</i>	3	82.1	(Wang et al., 2016b)
Respiratory syncytial virus pneumonia		<i>Respiratory syncytial virus</i>	3	82.1	(Wang et al., 2016b)
Staphylococcus aureus infection		<i>Staphylococcus aureus</i>	2.2	60.2	(Cilloniz and Torres Antonio, 2016; Loebinger and Wilson, 2012; Scott et al., 2008) (mean value)
H Influenzae type b pneumonia		<i>Haemophilus influenzae type b</i>	2.1	57.5	(Wang et al., 2016b)
		<i>unknown etiology</i>	19	520.0	
Diarrhoe	1312.1				
Rotaviral enteritis		<i>Rotavirus</i>	15.2	199.4	(Wang et al., 2016b)
Shigellosis		<i>Shigella spp.</i>	12.5	164.0	(Wang et al., 2016b)
Other salmonella infections		<i>Salmonella spp.</i>	6.9	90.5	(Wang et al., 2016b)
Enterotoxigenic E. coli infection		<i>Enterotoxigenic E. coli</i>	5.6	73.5	(Wang et al., 2016b)
Adenovirus		<i>Adenovirus</i>	5.4	70.9	(Wang et al., 2016b)
Cholera		<i>Vibrio cholerae</i>	5.2	68.2	(Wang et al., 2016b)
Amoebiasis		<i>Entamoeba histolytica</i>	5.2	68.2	(Wang et al., 2016b)
Cryptosporidiosis		<i>Cryptosporidium</i>	4.9	64.3	(Wang et al., 2016b)
Aeromonas		<i>Aeromonas spp.</i>	4.3	56.4	(Wang et al., 2016b)
Astrovirus infection		<i>Astrovirus</i>	3.0	39.4	(Desselberger and Gray, 2013; Elyan et al., 2014; Higgins et al., 2012; Lanata et al., 2013)
Campylobacter enteritis		<i>Campylobacter spp.</i>	2.9	38.1	GBD 2015
Giardiasis		<i>Giardia lamblia</i>	2.7	35.4	Mean Value of in- and outpatients in (Fischer Walker et al., 2010; Lanata et al., 2013)
Norovirus		<i>Norovirus</i>	2.3	30.2	(Wang et al., 2016b)
Enteropathogenic E. coli infection		<i>Enteropathogenic E. coli</i>	0.9	11.8	(Wang et al., 2016b)
Clostridium difficile		<i>Clostridium difficile</i>	0.7	9.2	(Wang et al., 2016b)
Vibrio parahaemolyticus		<i>Vibrio parahaemolyticus</i>	0.4	5.2	(Fischer Walker et al., 2010)
		<i>unknown etiology</i>	21.9	287.3	

AIDS	1192.6	<i>Human immunodeficiency virus</i>	100	1192.6	(Wang et al., 2016a)
Tuberculosis	1112.6	<i>Mycobacterium tuberculosis</i>	100	1112.6	(Wang et al., 2016a)
Malaria	730.5				(Wang et al., 2016a)
		<i>Plasmodium falciparum</i>	99	723.2	(World Health Organization, 2016)
		<i>Plasmodium vivax</i>	1	7.3	(World Health Organization, 2016)
Meningitis	379.2				(Wang et al., 2016a)
Pneumococcal meningitis		<i>Streptococcus pneumoniae</i>	30.0	113.8	(Wang et al., 2016a)
H. influenzae type b meningitis		<i>Haemophilus influenzae type b</i>	18.9	71.7	(Wang et al., 2016a)
Meningococcal meningitis		<i>Neisseria meningitidis</i>	19.3	73.2	(Wang et al., 2016a)
Listeriosis		<i>Listeria monocytogenes</i>	8.0	30.3	(Loeb et al., 2011; Pleger, 2011; Zueter and Zaiter, 2015)
		<i>Group B Streptococcus</i>	12.5	47.4	(Pleger, 2011; Zueter and Zaiter, 2015)
		<i>unknown etiology</i>	11.3	42.8	
Liver cancer due to hepatitis B	263.1	<i>Hepatitis B virus</i>	100	263.1	(Wang et al., 2016a)
Intestinal infection	178.5				(Wang et al., 2016a)
Typhus		<i>Salmonella typhi</i>	83.3	148.7	(Wang et al., 2016a)
Paratyphus		<i>Salmonella paratyphi</i>	16.3	29.1	(Wang et al., 2016a)
		<i>unknown etiology</i>	0.4	0.7	
Encephalitis	149.5	<i>unknown etiology</i>	100	149500.0	(Wang et al., 2016a)probably mostly (herpes simplex) viruses(Davies et al., 2006; Glaser et al., 2006)
Liver cancer due to hepatitis C	137.8	<i>Hepatitis C virus</i>	100	137.8	(Wang et al., 2016a)
Syphilis	106.8	<i>Treponema pallidum</i>	100	106.8	(Wang et al., 2016a)
Hepatitis	105.8				(Wang et al., 2016a)
Hepatitis A		<i>Hepatitis A virus</i>	10.6	11.2	(Wang et al., 2016a)
Hepatitis B		<i>Hepatitis B virus</i>	61.8	65.4	(Wang et al., 2016a)
Hepatitis C		<i>Hepatitis C virus</i>	2.4	2.5	(Wang et al., 2016a)
Hepatitis E		<i>Hepatitis E virus</i>	25.2	26.7	(Wang et al., 2016a)
Measles	73.4	<i>Measles virus (rubeola virus?)</i>	100	73.4	(Wang et al., 2016a)
Whooping cough	58.7	<i>Bordetella pertussis</i>	100	58.7	(Wang et al., 2016a)
Tetanus	56.7	<i>Clostridium tetani</i>	100	56.7	(Wang et al., 2016a)
Leishmaniasis	24.2	<i>Leishmania spp.</i>	100	24.2	(Wang et al., 2016a)
Dengue fever	18.4	<i>Dengue virus</i>	100	18.4	(Wang et al., 2016a)
Rabies	17.4	<i>Rabies virus</i>	100	17.4	(Wang et al., 2016a)
Chags disease	8	<i>Trypanosoma cruzi</i>	100	8.0	(Wang et al., 2016a)
Varicella and herpes zoster	6.4	<i>Varicella-Zoster-virus</i>	100	6.4	(Wang et al., 2016a)
Ebola virus disease	5.5	<i>Ebola virus</i>	100	5.5	(Wang et al., 2016a)
Yellow fever	5.1	<i>Yellow fever virus</i>	100	5.1	(Wang et al., 2016a)

Schistosomiasis	4.4	<i>Schistosoma spp.</i>	100	4.4	(Wang et al., 2016a)
Otitis media	3.9	<i>unknown etiology</i>	100	3.9	Most important pathogens: Respiratory syncytial virus, Corona virus, Streptococcus pneumoniae but in most cases viral-bacterial co-infections (Massa et al., 2009)
African trypanosomiasis	3.5	<i>Trypanosoma brucei</i>	100	3.5	(Wang et al., 2016a)
Upper respiratory infections	3.1	<i>unknown etiology</i>	100	3.1	Most cases probably caused by (rhino-) viruses (Dasaraju and Liu, 1996)
Intestinal nematode infections	2.7	<i>Acariasis</i>	100	2.7	(Wang et al., 2016a)
Diphtheria	2.1	<i>Corynebacterium diphtheriae</i>	100	2.1	(Wang et al., 2016a)
Cystic echinococcosis	1.2	<i>Echinococcus granulosus sensu lato</i>	100	1.2	(Wang et al., 2016a)
Gonococcal infection	0.7	<i>Neisseria gonorrhoeae</i>	100	0.7	(Wang et al., 2016a)
Cysticercosis	0.4	<i>Taenia solium</i>	100	0.4	(Wang et al., 2016a)
Chlamydial infection	0.2	<i>Chlamydia trachomatis</i>	100	0.2	(Wang et al., 2016a)
Other infectious diseases	119.6	<i>unknown etiology</i>	100	119.6	(Wang et al., 2016a)
Total number of casualties	8820.8				
Cases of unknown etiology	1127.0				

DIARRHEAL DISEASES AND LOWER RESPIRATORY TRACT INFECTIONS

In 2015 diarrheal diseases resulted in 1.3 million casualties (Wang et al., 2016a). They are caused by a variety of viral and bacterial pathogens that cannot always be identified. The GBD 2015 supplement (Wang et al., 2016b) provides some insight in 72% of the cases. Most important is the *rotavirus* with about 200 000 casualties but in almost 370 000 cases the provoking agents remain unidentified. By conducting a literature research on typical diarrheal pathogens and their share of infections and causes of deaths in other recently published studies about 80 000 of these cases are assigned to *Astrovirus*, *Giardia lamblia* and *Vibrio parahaemolyticus* (Table 1), but for 290 000 casualties no probably provoking pathogen could be nominated.

For lower respiratory tract infections, the data situation is worse in several aspects. They demand the most death victims worldwide. In 2015 these were 2.7 million, with 1.5 million casualties caused by *Streptococcus pneumoniae* alone. But the elucidation of the remaining cases is even more difficult compared to the diarrheal diseases, because for lower respiratory tract infections

there are 100 possible pathogens (Graffelman et al., 2004) and the GBD supplement provides only information on three of them. For three other notorious known pathogens an estimated guess can be performed by a literature study, but the cause of death remains unsolved for more than half a million deceased persons.

OTHER INFECTIONS

Concerning other infections Malaria and Meningitis are the next most important diseases with a total of more than 1.2 million annual casualties but only 50 000 cases of unknown etiologies. For some infections, like encephalitis, no pathogen share could be assigned at all, but the absolute number is at least smaller compared to unsolved respiratory infections or diarrheal diseases.

RESULTS AND DISCUSSION

The total number of pathogen casualties in Table 1 is 8.8 million. For about 1.1 million thereof no provoking pathogen could be identified, but for 7.7 million an assumed pathogen was assigned. The most important pathogen is *Streptococcus pneumoniae* with an estimated 1.6 million

Table 2. Pathogens and estimated number of deaths for 2015

Pathogen(s)	Estimated casualties [Thousands]
<i>Streptococcus pneumoniae</i>	1629.9
<i>Human immunodeficiency virus</i>	1192.6
<i>Mycobacterium tuberculosis</i>	1112.6
<i>Plasmodium falciparum</i>	723.2
<i>Mycoplasma pneumoniae</i>	273.7
<i>Hepatitis B virus</i>	328.5
<i>Rotavirus</i>	199.4
<i>Shigella spp. (without S. typhi and S. paratyphi)</i>	164.0
<i>Salmonella typhi</i>	148.7
<i>Legionella spp.</i>	145.0
<i>Hepatitis C virus</i>	140.3
<i>Haemophilus influenzae type b</i>	129.1
<i>Treponema pallidum</i>	106.8
<i>Salmonella spp.</i>	90.5
<i>Influenza virus</i>	82.1
<i>Respiratory syncytial virus</i>	82.1
<i>Enterotoxigenic E. coli</i>	73.5
<i>Measles virus</i>	73.4
<i>Neisseria meningitidis</i>	73.2
<i>Adenovirus</i>	70.9
<i>Vibrio cholerae</i>	68.2
<i>Entamoeba histolytica</i>	68.2
<i>Cryptosporidium</i>	64.3
<i>Staphylococcus aureus</i>	60.2
<i>Bordetella pertussis</i>	58.7
<i>Clostridium tetani</i>	56.7
<i>Aeromonas spp.</i>	56.4
<i>Group B Streptococcus</i>	47.4
<i>Astrovirus</i>	39.4
<i>Campylobacter spp.</i>	38.1
<i>Giardia lamblia</i>	35.4
<i>Listeria monocytogenes</i>	30.3
<i>Norovirus</i>	30.2
<i>Salmonella paratyphi</i>	29.1
<i>Hepatitis E virus</i>	26.7
<i>Leishmania spp.</i>	24.2
<i>Dengue virus</i>	18.4
<i>Rabies virus</i>	17.4
<i>Enteropathogenic E. coli</i>	11.8
<i>Hepatitis A virus</i>	11.2
<i>Chlostridium difficile</i>	9.2
<i>Trypanosoma cruzi</i>	8.0

<i>Plasmodium vivax</i>	7.3
<i>Varicella-Zoster-virus</i>	6.4
<i>Ebola virus</i>	5.5
<i>Vibrio parahaemolyticus</i>	5.2
<i>Yellow fever virus</i>	5.1

annual casualties. Subsequent representatives in the list of most deadly pathogens are *Human immunodeficiency virus*, *Mycobacterium tuberculosis* and *Plasmodium falciparum*, causing 1.2, 1.1 and 0.7 million further deaths in 2015. These four pathogens claim more than 50% of all 8.8 million casualties. A list containing all pathogens (responsible for more than 5000 casualties) is displayed in Table 2.

It might be surprising, that some of the most well-known notorious diarrheal pathogens like *Vibrio cholerae* or *E. coli* seem to be of minor importance. Reasons might be the plurality of other diarrhea provoking agents, especially *rotavirus* as well as the enhancement of worldwide sanitary measures and improved drinking water supplies within the last decades.

Finally it should be emphasized, that all these numbers are estimations lacking high precision. The GBD 2015 values providing the basis for this evaluation were regarded as fixed and flawless, but actually they have large uncertainties and the same is true for the complementations and estimations we provided. Nevertheless, to our knowledge these numbers are the best and most precise that exist for this kind of discussion.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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