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# Perspectives, Constructs And Methods In The Measurement Of Multimorbidity And Comorbidity: A Critical Review

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## Abstract

**Background:** There is no question about the importance of measuring multimorbidity and comorbidity. However, reviews of measures of multimorbidity/comorbidity are limited to multimorbidity indices that are used to predict mortality, disability, health-related quality of life and healthcare costs at individual level. **Objective:** To describe the perspectives, constructs and methods used in the measurement of multimorbidity and comorbidity. **Methods:** A structured literature search for studies reporting the measurement of multimorbidity or comorbidity was conducted in Medline and Embase. The references of the identified papers were consulted without restriction. The methods used by other researches that have reported on multimorbidity and comorbidity were also reviewed. The findings of the review are summarized under major constructs of multimorbidity and comorbidity. **Results:** Multimorbidity/comorbidity measurements involve the consideration of several perspectives. The four major constructs of multimorbidity/comorbidity measurement are magnitude, severity, pattern and burden. There are two major approaches of measuring multimorbidity and comorbidity. The first approach reduces measurements of multiple diseases to a single condition and the second approach uses clustering of diseases and cases in to relevant non-random groups. **Conclusion:** The measurement of multimorbidity involves multiple perspectives, constructs and methods.

## INTRODUCTION

Multimorbidity and comorbidity are person-level constructs that are commonly used to describe the co-occurrence of two or more disease conditions in an individual. Both constructs describe the presence of more than one condition in an individual. The key distinction between the two terms is the index disease. While multimorbidity is considered as the simple coexistence of two or more diseases in an individual where one disease is not necessarily more central than the other(s), comorbidity is usually defined as existence or occurrence of any distinct additional Nosological entity in a patient with an index disease (1, 2).

Measurement of Multimorbidity and comorbidity affects all variable axes that are considered in public health research: Confounder, modifier, exposure or outcome. All multimorbidity measurements rely on medical record information, patient self-report, clinical judgment, or large administrative databases. Multimorbidity and comorbidity are currently more prevalent in older people (3). Coexistence of diseases also challenges the current models of disease

prevention, treatment and care which are basically designed for single diseases rather than combination of diseases (4). From public health management perspective, appropriate management of Multimorbidity and comorbidity maximizes effectiveness and efficiency (5).

There is no question about the importance of measurement of multimorbidity and comorbidity. However, most reviews of measurement of multimorbidity and comorbidity are limited to comorbidity/multimorbidity indices despite the presence of several other relevant dimensions of multimorbidity and comorbidity. The basic epidemiological measurements and indicators that are applicable to multimorbidity and comorbidity are not well stipulated in a systematic manner. Those basic epidemiological measurements only exist in specific study reports only. Reviewing the available measurements will advance the understanding and management of multimorbidity and comorbidity.

In light of this, the envisaged study is designed to describe the epidemiological measurements of multimorbidity and

comorbidity. It describes the perspectives, constructs and methods used in the measurement of multimorbidity and comorbidity. The findings are expected to be useful in understanding the different axes of multimorbidity that can be measured and the set of methods that can be used in the measurement.

## **METHODS**

There were three stages of search and review strategies applied in this review. Firstly, a structured literature search for studies reporting the measurement of multimorbidity or comorbidity was conducted in Medline and Embase databases using the key terms “Multimorbidity” or “Comorbidity” and “Measur\$.” Due to a significant number of outputs the search was limited to the title of the studies. The references of the identified papers were consulted without restriction to identify additional articles.

A second search with “snowball” technique was used to identify original research reports that have applied the measurement of multimorbidity and/or comorbidity in their methodology. The methods used by these studies that have reported on multimorbidity and comorbidity were carefully reviewed. Though more focus was given to the methods and result sections of these papers, other relevant sections were also reviewed as appropriate.

The third structured search in Medline and Embase was specifically targeted at identifying review articles that address the measurement of multimorbidity and/or comorbidity. These were very limited in number but provided a summarized picture of the measurement. The entire content of these reviews was carefully scrutinized to understand the measurements of comorbidity and/or multimorbidity that were reviewed.

In overall terms, the results of the first search strategy were focused on the design of measurements of multimorbidity and/or comorbidity. The results of the second illustrate how those measurements were applied to specific studies. The third stage identified a comparative and summarized view of the measurement of multimorbidity/comorbidity.

Relevant concepts were extracted from the identified studies. Qualitative synthesis was used to summarize the concepts. The findings of the review from the three stages are integrated and summarized under major constructs/themes of multimorbidity and comorbidity. The perspectives of measurement and the general approaches used are also

discussed. The methods used to measure multimorbidity and comorbidity were illustrated using tables and formula. A few concepts from the measurement of global burden of disease were also reviewed.

## **RESULTS**

### **EPIDEMIOLOGICAL PERSPECTIVES**

There are six main perspectives that should be considered in the measurement of multimorbidity and comorbidity. First, the Nosological perspective, the classification of diseases, is important in defining the boundaries between disease entities that are of interest. Second, the etiological perspective, the causes of the co-existence of the diseases, is useful to establish meaningful relationship between the diseases (6, 7). Third, the chronological perspective, both the time sequence of occurrence of diseases and time span of assessment, is critical in the analysis and interpretation of multimorbidity and comorbidity data (8).

Fourth, the reference population considered in the measurement of multimorbidity and comorbidity can affect the results. A measurement of multimorbidity or comorbidity may consider the total population or sub-populations with a specific disease. Fifth, the orientation of the health system under which measurements are conducted can influence the selection of the index disease in comorbidity measurement. Finally, the professional orientation of the measurement – epidemiological/public health, clinical, or management – could affect the measurement, interpretation, and utilization of multimorbidity and comorbidity data (8).

### **GENERAL APPROACHES**

Different aspects of multimorbidity and comorbidity can be measured from different perspectives. This review focused on measurements of magnitude, severity, pattern and burden of multimorbidity and comorbidity. When there are differences between the measurements of multimorbidity and comorbidity, these are highlighted under each section. Central to the analysis of any multimorbidity and comorbidity data is the case-by-disease matrix. In this matrix, cases make the rows and diseases make the columns.

There are two major approaches in the measurement of multimorbidity and comorbidity. The first and the most common approach is reduction of the measurement values of the coexisting diseases in to a single summary variable that can undergo any analysis similar to single disease conditions. In this approach, disease counts, severity

weights, risk of death, proportion of life years lost, and disability weights of the coexisting diseases are combined in to a single summary variable. The second approach treats the coexisting diseases as multiple entities and tries to identify non-random clusters based on similarities and proximities. Cluster analysis and factor analysis are the main pattern analysis techniques that apply this approach. However, there were only few studies that have used these methods.

**MAGNITUDE OF MULTIMORBIDITY AND COMORBIDITY PREVALENCE**

There are many studies that have reported the prevalence of multimorbidity and comorbidity. The overall prevalence of multimorbidity is the proportion of people with multimorbidity (more than one disease) at the time (during the period) of measurement (9). This can also be limited to a specific set or number of diseases. In the case of measurement of prevalence of multimorbidity, a case-by-disease matrix of unweighted disease scores (disease present=1; disease absent=0) is used. Most of the indicators of prevalence of multimorbidity can be derived from this matrix.

Let’s consider there are m cases and n diseases in the table below. D is the total number of diseases for each case, obtained by adding the disease variables. T is the total number of disease events in the study population. It is a simple sum of the scores of all the diseases. Variable D is the most important variable in the measurement of prevalence of multimorbidity. The frequency (FREQ) table for the variable D is the main source of the prevalence indicators of multimorbidity.

**Figure 1**

Table 1: The case-by-disease matrix of multimorbidity (Prevalent cases)

	Disease 1	Disease 2	Disease 3	Disease 4	Disease n	Total (D)
Case 1	0	1	0	0	1	2
Case 2	0	0	0	1	0	1
Case 3	1	0	1	0	0	2
Case 4	1	0	1	1	0	3
Case m	0	0	0	1	1	2
Total	2	1	2	3	2	T

The main measures of prevalence of multimorbidity are:

Overall = [m-FREQ (D=1)]/m

Any Y diseases = FREQ (D=Y)/m; given Y>2

Y specific diseases=FREQ of Y in sum of specific diseases/m

More than Y diseases = 1- Cumulative FREQ (D<Y) (cumulative FREQ in proportion)

Average number of diseases per person = T/m

The prevalence of comorbidity measures the proportion of people with the index disease who have comorbid disease(s) (10). Note that the reference population is people with the index disease. The prevalence of comorbidity may be specific to a single comorbid disease, or a defined set of multiple comorbid diseases. The same method used in the prevalence of multimorbidity can be applied to prevalence of comorbidity, except that the index disease scores (which should be present=1 for all cases) are not included in summation of the scores to obtain D. As one additional disease coexisting with the index disease is enough to define a comorbidity, the overall prevalence of comorbidity will be [m-FREQ (D=0)]/m. Once the study subjects are limited to those with the index disease and scores of the index disease are not added to the total score, calculation of all the other indicators of prevalence of comorbidity will be similar to that of multimorbidity.

For two co-occurring diseases, the prevalence of multimorbidity and comorbidity can be estimated from the prevalence ratio (11) and the prevalence of one of the diseases in the general population. Consider the following two-by-two table for the prevalence of two diseases.

**Figure 2**

Table 2: Two-by-two table for prevalence of two diseases

		Disease 2		
		Present	Absent	Total
Disease 1	Present	a	b	a+b
	Absent	c	d	c+d
	Total	a+c	b+d	n

The prevalence of multimorbidity among all cases from the above 2X2 table is the number of cases with both diseases (a) divided by the total number of cases (a+b+c). If the total population is considered as a reference, the prevalence of multimorbidity will be a/n. on the other hand, the prevalence of comorbidity (disease 2) among those with the index disease (disease 1) will be a/(a+b). If the prevalence ratio (PR) of prevalence of disease 2 among those with disease 1 as compared to those without it is known, the prevalence of

comorbidity ( $P_c$ ) will be:  $P_c = PR * P_2$  where  $P_2$  is the prevalence of disease 2 among those without disease 1 ( $c/(c+d)$ ).

**INCIDENCE**

The incidence of multimorbidity is the development at least two disease entities in a healthy individual or the development of at least one additional disease in an individual with a pre-existing disease (12). The same case-by-disease matrix for incident diseases and incident cases can be used to measure the incidence of multimorbidity. The final score for analysis in this case will be the difference between the total score for new diseases (D) and the score of pre-existing diseases at baseline (B).

**Figure 3**

Table 3: Case-by-disease matrix of multimorbidity (incident cases)

	B	Disease 1	Disease 2	Disease 3	Disease n	D	D-B
Case 1	1	0	1	0	0	1	0
Case 2	0	0	0	0	1	1	1
Case 3	1	1	0	1	0	2	1
Case 4	0	1	0	1	1	3	3
Case m	0	0	0	0	1	1	1
Total		2	1	2	3	8	

Let’s consider that  $m_1$  and  $m_2$  are the number of cases with pre-existing disease and without pre-existing disease respectively, and  $m$  is the total number of new diagnoses. The main incidence indicators of multimorbidity will be:

In those with pre-existing disease) =  $[m - \text{FREQ}(D-B=0)]/m_1$

In those without pre-existing disease) =  $[m - \text{FREQ}(D-B < 2)]/m_2$

Any Y diseases =  $\text{FREQ}(D-B=Y)/m$ ; for  $Y > 2$

Y specific diseases =  $\text{FREQ}$  of Y in D-B of specific diseases

More than Y diseases =  $1 - \text{Cumulative FREQ}(D-B < Y)$ ; cumulative FREQ is in proportions

Average number of new disease per person =  $D-B \text{ total} / m$

The incidence of comorbidity is the development of comorbid condition(s) among people with an index disease (13). A similar case-by-disease matrix and indicators as the prevalence of comorbidity can be used but in this case with incident cases of comorbid conditions.

For two diseases, disease 1 and disease 2, the incidence of

multimorbidity is the sum of the incidence of disease 2 among those with disease 1, the incidence of disease 1 among those with disease 2, and the incidence of disease 1 and 2 (both newly diagnosed during follow up period) among those free from disease 1 and disease 2 at baseline.

For the incidence of a single comorbid disease, the two-by-two table will be useful. The incidence of the comorbidity will be  $a/a+b$ . The relative comorbidity risk (RcR) of the comorbid disease can be computed using the same method as exposure and disease relationships ( $RcR = [a/(a+b)/c/(c+d)]$ ). This relative risk shows the risk of the comorbid disease among those with the index disease as compared to those without the index disease.

**Figure 4**

Table 4: Two-by-two table for incidence of comorbidity

		Comorbid disease		
		Present	Absent	Total
Index disease	Present	a	b	a+b
	Absent	c	d	c+d
	Total	a+c	b+d	n

**SEVERITY OF MULTIMORBIDITY AND COMORBIDITY**

The severity of multimorbidity in an individual is usually measured using the Multimorbidity index. Several indices have been developed to measure the severity of multimorbidity (14). There are three main principles in the application of multimorbidity indices. First, a specific severity weight is assigned to each disease condition. Second, the severity weights (Sw) of coexisting diseases are ‘summed up’ to make the index score for each patient. Third, the index score is used to predict mortality, health-related quality of life and healthcare costs.

**Figure 5**

Table 5: The case-by-disease matrix of multimorbidity index

	Disease 1 (Sw1)	Disease 2 (Sw2)	Disease 3 (Sw3)	Disease 4 (Sw4)	Disease n (Swn)	Index
Case 1	0	1.5	0	0	3	4.50
Case 2	0	0	0	2	0	2.00
Case 3	4	0	4.01	0	0	8.01
Case 4	2	0	3.68	1	0	5.68
Case 5	0	0	0	2	2.5	2.00
Case m	1	0	0	0	0	1.00

A comorbidity index reduces the severity weights of all the coexistent illnesses and conditions to a single numeric score, thus allowing comparison of scores among patients (15). Multimorbidity indices are multiple item predictive indices

with three elements: items, a severity scale (including criteria), and a scoring system (16). The four commonly used generic multimorbidity indices are the cumulative illness rating scale (CIRS), the Kaplan–Feinstein Classification (KFC), the Charlson Comorbidity Index (CCI), and the Index of Co-Existent Disease (ICED). There are several other disease specific scores. Data sources vary based on the type of multimorbidity index used (17).

The choice of the appropriate and applicable multimorbidity index depends on four issues: the type and completeness of information; the type of score; the distribution of scores; and consideration of general versus specific disease (15). The severity weights of diseases are generally assumed to be additive in all the multimorbidity indices. However, this has to be tested using appropriate tests of additivity for every dataset before summing up the scores.

The resulting summary score is used as a predictor of mortality, quality of life and healthcare costs. It can also be considered as an outcome variable in a model that has different predictors of severity of disease. Depending on the preferred method of analysis the summary score may be categorized in to useful categories or may be considered as a continuous variable. Testing the distribution of the scores is also important if one considers parametric statistics in the analysis of the index.

The same principles apply to severity of comorbid conditions. The differences are the consideration of people with the index disease only and the exclusion of the severity weight of the index disease from the summation. The resulting index will be the severity index of the comorbid conditions only.

## **PATTERNS OF MULTIMORBIDITY AND COMORBIDITY**

Analysis of multimorbidity patterns can take two axes: The case axis and the disease axis. Two essentially similar methods for analysing patterns of multimorbidity are cluster analysis and factor analysis (18). Both methods yield clusters/components of cases/diseases with similar characteristics within them but different among them. Exploratory factor analysis and hierarchical cluster analysis with agglomerative algorithm are the common techniques used to identify non-randomly occurring components/clusters. The basic assumption behind is those units in the same cluster/group have the same underlying construct (19).

## **PATTERNS OF DISEASES**

The purpose of analysing the pattern of diseases is generally to identify relevant multimorbidity groups from a set of diseases (20, 21). The underlying characteristic for a cluster of diseases could be epidemiological, pathogenetic or management related similarities. Identification of diseases that tends to occur together has important clinical and public health implications (22).

## **PATTERNS OF CASES**

From the axis of cases, analysis of patterns using either cluster analysis or Q-factor analysis yields clusters of cases/patients with similar underlying disease conditions (23). The technique will identify sub-groups of populations of complex patients with specific combinations of coexisting diseases. The patterns of diseases within each group can then be described. This is important for more targeted management of patients with complexities.

Both cluster analysis and factor analysis can be used to identify non-random groups of cases and diseases. Commonly, cluster analysis is used for cases (rows) and factor analysis for variables (columns). But a dataset can be transposed to fit with either of the methods.

In case of patterns of comorbidities, the same techniques can be used. But the application of these methods will be limited to the comorbid conditions (additional diseases) among those people with the index disease.

## **BURDEN OF MULTIMORBIDITY OR COMORBIDITY MORTALITY RISK**

Disease-specific mortality risk, the number of deaths among people with a specific disease divided by the total cases of the same disease in a defined period, can be used to estimate mortality risk from multimorbidity/comorbidity. For the calculation of disease specific mortality risk, the number of deaths from a disease (the numerator) can be easily obtained from available data or can be estimated from the cause-specific mortality rate (CSMR). The total number of cases of the disease (the denominator) is usually available from reports or can be estimated from prevalence figures.

This disease-specific mortality risk (DSMR) shows the risk (probability) of death from a specific disease in an individual with that specific disease in a defined period. Deaths among cases of a disease can be due to the disease itself (confirmed deaths) or due to other causes (other cause of deaths). The

DSMR considers only the deaths that are due to or attributed to the disease.

**Figure 6**

Table 6: The case-by-disease matrix of disease-specific mortality risks

	Disease 1 (DSMR1)	Disease 2 (DSMR2)	Disease 3 (DSMR3)	Disease 4 (DSMR4)	Disease n (DSMRn)	DSMR total
Case 1	0	0.05	0	0	0.002	0.052
Case 2	0	0	0	0.02	0	0.02
Case 3	0.01	0	0.05	0	0	0.06
Case 4	0.10	0	0.12	0.05	0	0.27
Case 5	0	0	0	0.17	0.07	0.24
Case m	0.30	0	0	0	0	0.30

As death is a single time event, and there is usually one primary cause of death, risk of mortality of death from competing causes of death can be considered to be additive (cumulative). The fact that a single disease ultimately claims life even though other coexisting disease can have important roles favors additive approach. Assuming that competing risks of death are independent, the total risk of death of an individual from multimorbidity will be the sum of all the DSMRs of the coexisting diseases. This sum will be in the form of DSMR. This mortality risk will be unique to specific combinations of diseases i.e. the DSMR for a person with two diseases is different from a person with three and so on. In general:  $DSMR(\text{multimorbidity}) = DSMR_1 + DSMR_2 + \dots + DSMR_n$ .

The total DSMR multiplied by the number of cases of multimorbidity of the specified disease combination will provide the estimated number of deaths among those cases during a specified period. This number of deaths can be used to estimate the cause-specific mortality rate of the multimorbidity among the total population.

After the DSMR values are added, every individual with multimorbidity will have a single summary risk of mortality from all the diseases he or she have. The summary variable can be considered as an outcome variable for further analysis. However, it should be noted that a constant risk of mortality from coexisting diseases is assumed in the estimation of DSMR.

**POTENTIAL YEARS OF LIFE LOST (PYLL)**

Years of Life lost (YLL) due to death from a disease is the difference between life expectancy (LE) and age at death (24). Proportion of life years lost (PLL) due to premature death from a disease as calculated by dividing the YLL by LE ( $PLL = YLL/LE$ ) can be considered as an indicator of the

Severity of a disease in causing premature death. The YLL should be discounted and adjusted accordingly before being used for calculating PLL.

Assuming independence between coexisting diseases, there are two main possible approaches of combining PLL: additive approach and Multiplicative approach (25). The additive approach assumes the PLLs are additive. The PLL of a patient with multimorbidity will be the sum of the PLL of each of the coexisting diseases. The resulting PLL will be unique to specific combination of diseases.

With the same assumption of independence between coexisting diseases, the multiplicative approach provides an adjusted value that is less than the sum but greater than each of the individual diseases (26). In this approach, the PLL of multimorbidity will be between the PLL of the more severe disease and the sum of the PLL of all the co-occurring diseases. However, a synergy (interaction) factor may be considered if the assumption of independence is not considered. The general formula for the multiplicative approach is one minus the product of the complements of the weights:  $PLL(\text{multimorbidity}) = 1 - (1 - PLL_1) * (1 - PLL_2) * \dots * (1 - PLL_n)$

**Figure 7**

Table 7: The case-by-disease matrix for PLL

	Disease 1 (PLL1)	Disease 2 (PLL2)	Disease 3 (PLL3)	Disease 4 (PLL4)	Disease n (PLLn)	PLL (Combined)
Case 1	0	0.05	0	0	0.002	
Case 2	0	0	0	0.02	0	
Case 3	0.01	0	0.05	0	0	
Case 4	0.10	0	0.12	0.05	0	
Case 5	0	0	0	0.17	0.07	
Case m	0.30	0	0	0	0	

Once the PLL of the multimorbid situation is determined, it can be multiplied by the LE to find the YLL of the multimorbidity ( $YLL = PLL * LE$ ) (4). The resulting value can be multiplied by the total number of deaths in a specific age to estimate the PYLD at population level.

Expected years of survival (EYS) for an individual with multimorbidity can be estimated from the combined PLL of the coexisting diseases. The EYS is the difference between life expectancy (LE) and PYLL ( $EYS = LE - PYLL$ ).

**PREVALENT YEARS LIVED WITH DISABILITY (PYLD)**

Specific disability weights have been developed for different diseases (27). In the scale of disability weights, 1

corresponds to death and 0 shows ideal health free from any disease. The disability weights shows the fraction of years lived with the disease that are lost due to the effect of the disease. Assuming independence between coexisting diseases, the disability weights can be combined using the additive and multiplicative approach to estimate the disability weight (Dw) of a multimorbid condition. In the additive approach  $Dw_{(combined)} = Dw_1 + Dw_2 + \dots + Dw_n$ ; and in the multiplicative approach  $Dw_{(combined)} = 1 - (1 - Dw_1) * (1 - Dw_2) * \dots * (1 - Dw_n)$ .

**Figure 8**

Table 8: The case-by-disease matrix of PYLD

	Disease 1 (Dw1)	Disease 2 (Dw2)	Disease 3 (Dw3)	Disease 4 (Dw4)	Disease n (Dwn)	Dw (combined)
Case 1	0	0.05	0	0	0.002	
Case 2	0	0	0	0.02	0	
Case 3	0.015	0	0.135	0	0	
Case 4	0.14	0	0.120	0.05	0	
Case 5	0	0	0	0.06	0.070	
Case m	0.90	0	0	0	0	

The PYLD of multimorbidity can then be obtained by multiplying years lived with disability (YLD) by the combined disability weight. The total PYLD of multimorbidity at population level will be:  
 $PYLD = YLD * Dw * Prevalence$ .

Prevalent years lived in full health (PYLH) for an individual with multimorbidity can be estimated from the combined Disability of the coexisting diseases. The PYLH is the difference between total years lived with disability (TYLD) and PYLD ( $PYLH = TYLD - PYLD$ ).

Total years Lived in full health (TYLH) for an individual with multimorbidity can be estimated from EYS and PYLD. The TYLH is the difference between expected years of survival (EYS) and PYLD ( $PYLH = EYS - PYLD$ ).

### DISABILITY ADJUSTED LIFE YEARS (DALY)

The total burden of multimorbidity can determined by DALY, the sum of Potential Years of Life Lost (PYLL) and Prevalent Years Lived with Disability (PYLD) (28). The sum of DALYs for all individuals with the comorbidity during a year will constitute the total burden of the multimorbidity in a population. The DALY of multimorbidity will be the sum of PYLL and PYLD obtained in the above estimations:  $DALY = PYLL + PYLD$

Healthy life years (HLL) will be the difference between life expectancy and disability adjusted life years:  $HLL = LE -$

DALY. This will be the total number of healthy years that an individual is expected to live.

In the estimation of burden of comorbidities, the same principles of as the estimation mortality risks, PYLL, PYLD and DALY that are applied in multimorbidity can be used. But in this case, the estimation will be limited to the burden of comorbid conditions (additional diseases) among those people with the index disease.

### CONCLUSIONS

Multimorbidity and comorbidity measurements need the consideration of several perspectives of measurement. The four major constructs of multimorbidity/comorbidity measurement are magnitude, severity, pattern and burden. The two major approaches of measurement multimorbidity and comorbidity are reducing measures of multiple diseases to a single condition and clustering of diseases and cases in to relevant groups. The basic underlying principles in the measurement of multimorbidity and comorbidity are analogous with the main difference being the role of the index disease in comorbidity. Overall, measurements of multimorbidity and comorbidity involve multiple perspectives, constructs and methods.

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